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SUPPLEMENT

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Environmental tobacco smoke and ischaemic heart disease: a case study in applying causal criteria

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Contents

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Abstract ***Background:*** Whether ischaemic heart disease (IHD) is caused by exposure to environmental tobacco smoke (ETS), commonly known as "passive smoking", has been debated from both epidemiological and biological perspectives. ***Methods and results:*** In this paper we use Bradford Hill criteria to synthesize results from the biological and epidemiological literature in a formal assessment of the strength of support for such a relationship. Although we find that these criteria, designed for clinical trials, do not give an ideal framework for assessment of epidemiological and biological studies, nevertheless they do provide systematic guidance for this assessment. For the general population, of the nine tests proposed by Hill we find that one (biological plausibility) seems to be supported, though not unarguably; three (strength, consistency, specificity) appear to fail by accepted standards; and the remaining five have insufficient data for a clear evaluation (biological gradient, experimental evidence, temporality, coherence, analogy). Overall, this provides at best weak support for a causal association between ETS and IHD across the general community. Conversely, there appears to be more support, especially in the biology studies, for an association between ETS and IHD for those with pre-existing disease, although epidemiological studies are limited in this area. ***Conclusions:*** One of the outcomes of this review is the identification of areas of focus for future epidemiological and biological research. First, we find that stronger associations may be found in the particular subpopulation with pre-existing IHD. In this case, more convincing biological plausibility and experimental evidence indicate a need for relevant epidemiological studies, although individual responses are very variable. Second, we identify the need for further, more detailed evaluations of the nature of vessel wall thickenings occurring in experimental models of ETS exposure. Third, we propose long-term animal studies of initiation of IHD, including direct assessment of effects

on the accumulation of lipid in vessel walls, at appropriate ETS exposure levels.

Short abstract We use Bradford Hill criteria to synthesize the biological and epidemiological literature so as to assess formally whether ischaemic heart disease (IHD) is caused by exposure to environmental tobacco smoke (ETS). For the general population we find, at best, weak support for causality: of nine tests, one (biological plausibility) is supported, though not unarguably; three (strength, consistency, specificity) fail; and five (biological gradient, experimental evidence, temporality, coherence, analogy) have insufficient data for clear evaluation. For the population with pre-existing IHD the biological support is possibly stronger. We identify three areas for future research: epidemiological studies of those subpopulations with pre-existing IHD; evaluation of the nature of vessel wall thickenings occurring in experimental studies; and long-term animal studies of initiation of IHD, including direct assessment of effects on the accumulation of lipid in vessel walls, at appropriate ETS levels.

Key words Passive smoking · ETS · Review · Causality

Summary

The causal argument: general population

Within Hill's framework, forced though it may sometimes appear for epidemiological studies, we have considered substantial sets of data related to the possible causal association of IHD and exposure to ETS. On the basis of the analyses in this paper we have drawn the following conclusions for the overall population exposed to ETS:

1. There is a reasonable case for biological plausibility of a causal association. This is, however, a weak test and one that is usually passed in any context where study has been seen as worthwhile.
2. The experimental data do not strongly support the association. At best there is a possibility, however, of aggravation of existing IHD as discussed below.
3. The overall strength of association, however one calculates it, is well under the level that supports causality, especially after allowance for bias is made. We have demonstrated that the overall RR estimate of 1.24 for mortality may be reduced after accounting for publication bias alone, and both estimates for mortality and morbidity may be further reduced after accounting for other biases. All of these estimates are below the values of 1.5–3 and above, seen as close to "strong" by various authorities in the field, and after such adjustment for bias they may not be statistically significant at the 5% level.
4. The exposure-response argument is not established as indicated by our evaluation.
5. The consistency argument is not clear-cut.
6. There is clearly a lack of specificity in this area, and this seems to be universally acknowledged. Although (unlike many authors) we do not feel that a lack of specificity of itself means that a relationship is not causal, it does mean that a very serious attempt to consider possible confounding is needed.
7. The analogy criterion and the coherency criterion present substantial problems. It appears to us that the effects of active and passive smoke are well documented as being very different in this area, and this lack of analogy may explain the lack of coherence acknowledged by most authors.

The interpretation of fulfilment of Hill's criteria is somewhat subjective. Glantz and Parmley [11] and Law et al. [13] review epidemiological studies concerned with the association between ETS and IHD and provide an overview of the various biological mechanisms that might cause this association, and they accept without further evaluation the assertion by Wells [15] and Kristensen [163] that the link is causal. The report of the Australian NH&MRC [6] (Table 6.6) evaluates the status of the various criteria and, despite acknowledging that the criteria are at best weakly met in some areas, nonetheless still concludes that an excess risk caused by exposure to ETS has been demonstrated.

Our contribution is to provide a much more detailed critique of the available material, both biological and epidemiological, and in our opinion, this leads to perhaps one of the nine tests being passed (biological plausibility), perhaps five about which there is insufficient or mixed evidence (biological gradient, experimental evidence, coherence, analogy, temporality) and three that we believe are actually failed (strength, consistency, specificity). Overall, this seems to us to indicate that one can at most say there is very weak support at the current time for this association across the general population.

The causal argument: pre-existing IHD

For the particular subpopulation with pre-existing IHD we find that stronger associations may apply. Indeed, one of the strengths of this review is in distinguishing between such a group and the general population. We find:

1. The biological plausibility seen in the general situation is of course maintained in this sub-population.
2. The experimental data are more supportive of an effect in this sub-population; although the acute effects that can be demonstrated, such as endothelial loss and platelet aggregation, have an impact on the disease process that can only be conjectured, they are certainly consistent with a biological mechanism that would affect those with pre-existing disease.

3. There are no existing epidemiological data of which we are aware that will give information on the strength of association in this sub-population. It is possible that the observed relative risks could be a mixture of an association that is sufficiently strong to support causality in those with pre-existing conditions and the lack of such association in those without such conditions.
4. The exposure-response data are also consistent with a "threshold" effect, consistent with that described in the experimental data above.

By considering the experimental data, we are led in this situation to a plausible but as yet untested situation. We believe that it is reasonable on the data seen thus far to hypothesize that there may be real exacerbation of risk in those with pre-existing IHD. To prove this we clearly need different epidemiological studies than those we currently have available. The experimental data show that we need information on the real effect in populations who have pre-existing disease. For this one needs to consider the relative risk, or perhaps the survival time to the next incident, of such populations with both exposure and non-exposure to ETS. Although this is clearly a somewhat sensitive population on which to collect data, our analysis lends clear support to such further research as being worthwhile.

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1. Introduction

Over the past decade the existence and strength of a causal relationship between ischaemic heart disease (IHD) [which we take to include cardiovascular heart disease (CVD)] and exposure to environmental tobacco smoke (ETS) has been debated from both epidemiological and biological perspectives.

The United States Surgeon General [1] stated that "more detailed characterisation of exposure to ETS and specific types of CVD associated with this type of exposure are needed before an effect on the etiology of CVD can be established." After considering only two cohort studies [2, 3] the Australian National Health and Medical Research Council (NH&MRC) report [4] similarly stated that "only limited evidence exists for any increased risk of cardiovascular disease in passive smokers" but that "it is essential to pursue this question further". More recently, however, the United States Occupational Health and Safety Administration [5] and a new Australian NH&MRC report [6] concluded that the association between IHD and exposure to ETS was in fact a causal one, based on 14 published epidemiological studies and data from a number of biology and experimental studies.

It is the goal of this paper to evaluate on a systematic basis the contributions that the biology and epidemiology literature provide to overall scientific support for a causal relationship between exposure to ETS and IHD in adults. We employ explicitly the nine criteria proposed by Bradford Hill [7], which still stand as foundation-stones for causal inference. Our focus is on establishing whether the relationship between exposure to ETS and IHD in a population is actually causal. [As discussed by Tweedie and Mengersen (in preparation) and Greenland and Robins [8], among others, extra steps are needed to move to an assertion of causality in an individual].

Other reviews of this association have also been published [9–13]. The treatment we give herein is rather more detailed and brings together both the biology and the epidemiology literature in a formal assessment of the strength of support for such a causal relationship.

Our conclusions are not clear-cut. We find that in the general population the criteria are either unsatisfied or, at most, weakly satisfied, but in the particular subpopulation of those with pre-existing IHD there may be a rather stronger case and one that would appear to repay more attention in the epidemiological area.

Hill's criteria [7], as adopted in our context, are as follows. Note that we have varied Hill's original order so that these are more logically constructed for our purposes, and we have also grouped these so that the role of biological thinking and experimental results are differentiated from the more observational epidemiological criteria.

Biological criteria

1. **Plausibility**: is the proposed association explained by a biologically plausible mechanism?
2. **Experimental evidence**: are there experimental studies that support the association? If preventive action is taken because of an observed association, is the frequency of associated events reduced in subsequent studies?

In practice these criteria are intertwined. Typically, plausibility may hinge on the experimental material available, and then these two may well reinforce each other as time goes by more experimental evidence may make the association more plausible, leading to the impetus for collection of yet more evidence to elucidate the mechanisms involved. Care thus needs to be taken not to "double dip" in this aspect of proof.

Epidemiological criteria

3. **Strength**: if the relative risk is "strong", there is less likelihood that there are other adequate explanations of the observed association. In checking this criterion we will also need to consider the influence of chance, study quality, confounders and the possibility of publication bias.
4. **Biological Gradient**: is there an exposure-response relationship exhibited over the range of studies?
5. **Consistency**: is the association consistent over the various studies?
6. **Specificity**: is the association limited to the particular outcome? This criterion also demands that we again consider confounding factors as well as specificity of exposure and specificity of response.

Of course there is some overlap between these criteria. In particular, confounding is an aspect to be considered in both *strength* and *specificity of association* and, hence, also in *consistency*, and as in any epidemiological area where the measurement of level of exposure is difficult, it is easy to confuse the support for *strength of association* with the support for *biological gradient* [13].

Mixed biological and epidemiological criteria

7. **Temporality:** did the exposure precede the outcome?
8. **Analogy:** is the proposed relationship analogous to some other accepted cause and effect?
9. **Coherence:** does the proposed relationship seriously conflict with generally known facts about the natural history and biology of the disease?

In this case the standard analogy is with the relationship of active smoking with IHD, and coherence must also be considered in relation not just to other aspects of associations involving ETS but also to those involving active smoking. The interactions between the two criteria are then quite subtle.

In this paper we consider the first two of Hill's criteria in light of the available biological evidence, the next four criteria from the standpoint of epidemiological studies, and the final three criteria on the basis of both biological and epidemiological evidence. We have set a cut-off date of the end of 1997 in this (revised) version of the review; clearly the picture changes in minor ways with each further study of the association, and regular updating is certainly to be encouraged.

Finally, our conclusions and a comparison with those drawn by others is given in the Discussion, where we also consider the social as well as the scientific relevance of the issues involved.

2. Biological criteria

The generally accepted view of the development of IHD is that it is a multifactorial process with the potential for a large number of factors to initiate and aggravate the disease process, perhaps through just a few common pathways. Thus, the effects of different risk factors on the pathology cannot necessarily be distinguished from each other. Numerous experimental studies attempt to provide evidence for a role for ETS in IHD through many of the postulated pathways.

There is a substantial body of experimental literature that claims that ETS both initiates and increases the growth of atherosclerotic plaques and also aggravates pre-existing IHD by inducing ischaemia, increasing arterial wall reactivity, inducing arrhythmias and stimulating platelet aggregation and thrombus formation.

Several reviews have discussed this experimental evidence [5, 10–13, 15]. However, in most cases they have accepted the conclusions of the original papers without critically analysing the experimental design, techniques and interpretation of results. Below we evaluate the original articles so as to determine whether the conclusions are valid scientifically. For the purposes of this review we have divided those studies into two broad catogories: the first considers evidence relating to the initiation and progression of lesions and the second considers evidence relating to effects largely dependent on pre-existing lesions.

On the basis of the currently available literature and the examination we present in this review, we draw the following conclusions:

(a) There is no evidence that ETS stimulates the formation of new atherosclerotic plaques in humans or in animals. The evidence that ETS stimulates the growth of existing plaques is weak.
(b) ETS may contribute to small increases in vessel wall thickness in humans or may increase areas of lipid staining in animals under extreme experimental conditions, but it is not clear what these changes represent in terms of the human disease.
(c) ETS may impair endothelium-dependent vessel relaxation, possibly through decreased nitric oxide, but there is currently no evidence that ETS plays a causative role in the early stages of atherogenesis through this mechanism.
(d) There is no convincing evidence that exposure to ETS alters plasma lipid profiles to make them more atherogenic. Effects on LDL deposition in vessel walls have yet to be determined.
(e) ETS may increase the risk of thrombosis in persons with pre-existing cardiovascular disease by increasing the propensity of platelets to aggregate and by decreasing their sensitivity to anti-aggregatory prostaglandins. Effects on individuals are variable.
(f) ETS may reduce exercise tolerance in those with pre-existing disease. Healthy persons are typically not affected.
(g) Exercise-induced arrhythmias may occur in persons with pre-existing IHD and elevated carboxyhaemoglobin levels, but these high levels are unlikely to be reached by exposure to ETS.
(h) Exposure to high levels of ETS may increase the size of myocardial infarcts, but not necessarily the area at risk. There is evidence of a strong threshold effect in these outcomes.

Hence, we conclude that:

Test 1 (*plausibility*): there is a prima facie case for some biological plausibility of an association between ETS exposure and increased incidence of IHD through one of the several possible pathways discussed above and, especially, through (c) and (e)–(h). Further research is required before the route of this association, either direct or in collaboration with other risk factors, is identified.

However, plausibility is a rather weaker conclusion than the finding of convincing experimental evidence. In particular, the pathways for which there does seem to be some experimental evidence (thrombosis, reduced exercise tolerance, increased exercise-induced arrhythmias and increased infarction size) are related to those with pre-existing conditions, and there is much less evidence at this stage for pathways by which ETS might initiate rather than aggravate IHD.

Test 2 (*experimental evidence*): in the general population the experimental evidence for an association between ETS exposure and increased incidence of IHD is weak. In those with pre-existing IHD there is stronger experimental evidence that ETS may exacerbate or accelerate IHD through a number of mechanisms such as (c) and (e)–(h).

2.1. Initiation and development of lesions

Human studies

Two recent studies link ETS to an increase in intimal-medial thickening of the human carotid artery [16, 17]. Howard et al. [16] used B-mode ultrasound to measure wall thickness in over 12,000 participants aged 45–65 years. They reported an increased intimal-medial thickness in current smokers as compared with ex-smokers, which was greater than that found in never-smokers exposed to ETS, and this, in turn, was greater than that observed in never-smokers not exposed to ETS. The mean difference between never-smokers exposed and not exposed to ETS was very small (mean values 0.711 versus 0.700 mm, respectively). The differences were reported to be maintained after adjustment for diet, physical activity, body mass index, alcohol intake, education and major cardiovascular risk factors (difference 0.014 mm).

Our analysis of data extracted from Fig. 1 of Howard et al. [16] indicates that the slopes of the regression lines for ETS-exposed and ETS-unexposed groups are not significantly different, with the same increments in thickness occurring in the two groups with increasing age. Thus, the small increase in wall thickness was present at the beginning and remained unchanged over two decades despite exposure to ETS. This does not seem consistent with the hypothesis that the increase is due to ETS exposure.

Diez-Roux et al. [17] state in the abstract of their paper that passive smokers have thicker walls than non-exposed never-smokers. However, analysis of the data shows that there is no significant or consistent difference in wall thickness between the two groups, and this finding is acknowledged by the authors in their discussion.

Even if a significant increase had been demonstrated in these studies, the relevance to IHD is unclear, as in neither study did the authors address the nature of the wall thickening. Atherosclerotic plaques are dangerous when there is a thin fibrous cap overlying a grumous, necrotic core of extracellular lipid [18]. Ulceration and splitting of the thin fibrous cap leads to the formation of thrombi, which can break off, occlude distal vessels and lead to infarction. A thickened fibrous cap, however, is protective of clinical sequelae; thus, demonstration of increased intimal-medial thickness is not necessarily detrimental. Furthermore, the small increases in wall thickness described by Howard et al. [16] would likely have no effect on blood flow. Vessels with clearly thickened walls due to developing lesions compensate by increasing their luminal diameters such that blood flow is not impaired [19]. Only in advanced atherosclerosis is the luminal cross-sectional area significantly reduced

and blood flow compromised. It should be noted that the approximate 14-μm mean increase in carotid wall thickness shown by Howard et al. [16] is equivalent to the thickness of two smooth muscle cells or approximately $\frac{1}{50}$ of the total carotid wall thickness.

In a recent study, He et al. [20] report on the relationship between the number of stenotic coronary arteries and exposure to passive smoke in Chinese women. After adjustment for various risk factors the odds ratio for simple exposure (yes versus no) was 1.38 (95% CI from 0.67 to 2.81). Statistically significant odds ratios were found only for heavy exposure (>20 cigarettes/day, >25 years exposure) and severe disease (2 and 3 stenotic arteries). The corresponding 95% confidence intervals, however, were very wide due to small numbers (e.g. for >20 cigarettes/day and 3 stenoses the odds ratio is 7.01, with a 95% CI ranging from 1.01 to 48.96). Nevertheless, a strength of the study is that it measures an anatomical rather than a clinical endpoint. Although the data provide only weak evidence of an effect, further studies of this type might resolve whether or not ETS may aggravate the disease in a person with existing IHD through the thrombotic pathway (see below). A substantial number of cases (16/78) had a myocardial infarction, and it would be valuable to determine correlates for this sub-group.

It is possible that the ongoing study on pathological determinants of atherosclerosis in youth (PDAY) may provide some information relevant to passive smoking. There is a strong association between smoking and increased lesion coverage in the abdominal aorta and, to a lesser extent, in the right coronary artery [17], but the thiocyanate cut-off level of 90 μg/l was chosen to ensure detection of active smokers. It is not possible to draw conclusions about effects of exposure to ETS except to note that lesion thickness in coronary arteries was not always increased with active smoking [21]. There were, however, other significant changes such as increased Apo E deposition and increased macrophage involvement, which may be of greater significance than lesion thickness. It remains to be determined if these increases seen with active smoking take place at appropriate levels of ETS exposure.

We conclude that in humans (a) there is insufficient evidence available to determine whether exposure to ETS initiates the formation of new atherosclerotic plaques and (b) the proposition that such exposure exacerbates growth of existing plaques is only weakly supported.

Animal studies

Several studies report a positive effect of ETS on the development, but not the initiation, of atherosclerosis in animal models of the disease [22–26]. One study [27] reports no increase in atherosclerosis and a possible negative effect with reduced lesion development.

Penn and Snyder [22] exposed cockerels to sidestream smoke from a constant five cigarettes for 6 h per day, 5 days per week, from 6 to 22 weeks of age. They found no increase in the numbers of plaques in abdominal aorta and no change in their distribution but detected an increase in their size as determined by a plaque index, which is the mean cross-sectional area of plaque divided by the mean luminal circumference.

Several problems with this study have previously been identified [28, 29]. Apart from concerns over exposure levels [28], the plaque index does not provide an unambiguous measure of plaque size [29]. The plaque index does not necessarily reflect absolute changes in plaque size; even a slightly smaller average vessel diameter in the exposed as compared with the non-exposed group would result in an increase in the plaque index without an absolute increase in plaque size. Data are not provided on the sizes of vessels or, as a surrogate, the weights of the cockerels in the exposed and non-exposed groups. Moreover, a large difference in the number of animals in the 2 groups (30 exposed, 12 non-exposed) and a similar difference in the number of sampling sites (153 exposed and 50 non-exposed) may have introduced further bias. No photograph of the plaques is provided; thus, it is not possible to determine the nature of the plaques and whether they resemble the human disease.

The same criticisms apply to the paper by Penn et al. [23], who report that the smoke from a constant one cigarette, 6 h per day, 5 days per week for 16 weeks increased the plaque index in cockerels to about the same extent as five cigarettes in their earlier study. The same authors found that exposure of cholesterol-fed cockerels to 50–200 ppm carbon monoxide for 2 h per day, 5 days per week for 16 weeks had no effect on the plaque index [30].

Zhu et al. [24] used similar ETS exposure regimes to evaluate the influence of passive smoking on cholesterol accumulation within fatty streaks in the aortae and pulmonary arteries of cholesterol-fed rabbits. A "low-dose" group was exposed to ETS levels similar to that found in heavily smoking-polluted human environments, although high-dose group was exposed to levels several times higher. They reported that the percentage of surface area covered by Sudan IV-stained lipid deposits increased significantly in both vessels with a significant dose-response relationship (through ANOVA) for the two exposure levels. When the low-dose group, however, is compared independently with the control group the difference in lipid area is not significant, raising the possibility of a threshold effect. It should be noted that the fatty streaks observed in this study do not resemble human atherosclerotic plaques but instead more closely resemble the ubiquitous human juvenile fatty streak. (Among children aged 2–15 years, 99% have aortic fatty streaks. Although some streaks progress to become atheromatous, the majority disappear with time [31].)

In a further study the same group [26], using the same ETS-exposed rabbit model, investigated the effect of the

beta blocker metoprolol on the deposition of lipid in blood vessels, since clinical studies had suggested that beta-blockers might have a protective effect in smokers. No effect of metoprolol was found. This paper is of interest, however, because analysis of the regression lines on cholesterol exposure (measured as cholesterol-weeks) versus the percentage of surface area covered by lesions (their Fig. 2) indicate that the apparent increase in lesion cover with exposure to ETS may be accounted for, in large part, by the differences in cholesterol exposure (as shown in their Table 2).

The studies reporting that exposure to ETS promotes atherosclerotic lesion development are contradicted by a large study sponsored by the National Cancer Institute (USA) on cholesterol-fed beagle dogs exposed over a 2-year period to mainstream smoke from six cigarettes/day [27]. Neither mainstream smoke, with either high or low nicotine content, nor the addition of extra carbon monoxide resulted in increased lesion development or growth. Rather, the reverse occurred, with higher levels of exposure being associated with a reduced severity of atherosclerosis. Whereas the morphometric analysis can be criticised as are the others above for not being rigorous and free of subjective assessment, it is unlikely that a positive effect of ETS was missed.

Additional arguments claiming to support a role for ETS in the initiation and development of atherosclerotic lesions come from studies involving the injection into birds of polycyclic aromatic hydrocarbons (PAHs) [32-34]. These components of ETS are known to be carcinogenic. Studies by Benditt and Benditt [35] have shown that about 30% of human plaques are monotypic, that is, they are derived from small populations of cells with a selective proliferative advantage. This observation is consistent with a cellular transformation caused by a mutagen. The general finding in these avian studies was an increase in lesion size but no increase in number. No photograph was published of the histological sections; therefore, it is not possible to assess the form of the thickening and the relevance to human atherosclerosis. Also, the relevance either to human atherosclerosis or to exposure to ETS of the injection of birds with relatively high concentrations of carcinogens is rather unclear.

An important outcome of this review of the animal studies, as for the human studies, is the lack of detailed information on the morphometric features of intimal thickenings. This needs to be redressed especially to determine the extent to which the ETS-associated thickenings might be more or less fibrous than thickenings that develop in the absence of ETS exposure.

We conclude that there is no evidence that ETS stimulates the formation of new atherosclerotic plaques in animals. Some animal studies suggest that arterial wall thickness or areas of lipid staining may be increased marginally under extreme experimental stimuli, but it is not clear what these changes represent in terms of the human condition.

Potential mechanisms for arterial thickening

Numerous studies have attempted to provide evidence for mechanisms by which ETS might initiate the development and subsequent growth of plaques. Generally these studies centre around the response-to-injury hypothesis, or endothelial dysfunction, and the "lipid" hypothesis that exposure to ETS alters plasma lipid profiles. This evidence is considered next.

Davis and colleagues [36–39] have published a number of papers reporting that cigarette smoking results in an increase in the number of circulating endothelial cell carcasses; that is, ETS results in detachment of endothelial cells. Blood was obtained by venepuncture before and after the active smoking of two cigarettes and the number of desquamated endothelial cells was counted using a Neubauer chamber (standard haemocytometer). Cell counts approximately doubled from about 2 to 4. There was no correlation, however, between cell carcass count and plasma nicotine concentration or with carboxyhaemoglobin level. Most unfortunately, the authors did not routinely identify the cells as endothelium by staining with labeled antibodies to endothelium-specific markers. Increases in cell carcass number, albeit smaller, were also observed following the smoking of non-tobacco cigarettes. Exposure to passive smoking increased numbers of circulating cell carcasses from a mean of 2.8 ± 0.9 to 3.7 ± 1.1 [39]. A major concern with these studies is the accuracy of the low counts, given that ideally, no fewer than 100 cells should be counted in a haemocytometer.

The rationale for examining endothelial cell carcasses stemmed from the ideas of Ross and Glomset [40] that endothelial denudation was a primary stimulus for atherosclerosis. Ross [41] and other workers, however, have since shown that desquamation is a feature of advanced, but not early, disease and that in animal models the loss of endothelium needs to be substantial and contiguous for intimal thickening to occur [42].

Several studies show that active smoking impairs endothelium-dependent vasodilatation, although not irreversibly. After 12 months of abstinence the endothelial dysfunction caused by smoking is almost completely reversible [43, 44]. In a recent study by Celermajer et al. [45] the brachial artery diameters of young and healthy age- and sex-matched control, ETS-exposed and active smokers were measured using ultrasonography under baseline conditions, during reactive hyperemia (with flow increase causing endothelium-dependent dilatation) and after administration of nitroglycerin (an endothelium-independent dilator). They found flow-mediated dilatation in all control subjects (8.2 ± 3.1%; range 2.1–16.7) but observed significant impairment in passive smokers (3.1 ± 2.7%; range 0–9) and in active smokers (4.4 ± 3.1%; range 0–10). In the passive smoking group the impairment was inversely related to the degree of self-reported exposure to ETS. Dilatation induced by nitroglycerin was similar in all groups, indicating that the impairment was endothelium-dependent. The active and

passive smoking groups were not significantly different, with the passive smokers being slightly (but not significantly) worse off than the active smokers in spite of dramatic differences in salivary cotinine levels (smokers 170 ± 102 ng/ml; passive-smokers 3.7 ± 3.6 ng/ml; controls 1.2 ± 1.5 ng/ml). Salivary cotinine levels were not significantly correlated with flow- mediated dilatation on either univariate or multivariate analysis.

Celermajer et al. [45] state that the finding is "consistent with (but does not prove) a causative role for environmental tobacco smoke in the early stages of atherogenesis." They refer to the animal studies [22–24] in which ETS is claimed to induce atherosclerosis and assume that the mechanism for this induction is ETS-induced endothelial dysfunction.

Inhibition of NO exacerbates the formation of fatty streaks in the cholesterol-fed rabbit [46], and L-arginine partially inhibits the development of a myointimal thickening in the rabbit following balloon catheter-induced injury [47]. NO is not only a potent vasodilator but has an inhibitory effect on platelet adhesion and aggregation. It also inhibits monocyte adherence to endothelium, controls endothelial permeability and inhibits smooth muscle proliferation [48]. Thus, in theory, removal of NO through endothelial dysfunction could contribute to atherogenesis.

Other, more recent studies [49, 50] report similar effects of ETS on coronary and aortic diameters. ETS is shown in both studies to produce small but significant decreases in lumenal diameter. It is not clear, however, how these changes compare with the range of vessel responses encountered in response to normal physiological homeostatic mechanisms and if the ETS-induced decreases in diameter have a deleterious effect on perfusion. It would be important to determine the effects in vessels badly stenosed with atherosclerosis, that is, in persons with pre-existing IHD. In both studies, however, the baseline characteristics of the active and passive smokers are identical to those of the non-smokers.

In another study [51], common vascular measures of heart rate, blood pressure, cold pressor test, forearm vascular resistance and other measures such as sustained handgrip were not affected by short-term ETS, although sympathetic nerve activity did increase.

Some studies report alterations in plasma lipoprotein profiles in persons exposed to passive smoking. Pomrehn et al. [52] report in an abstract that children whose parents smoked daily had lower mean levels of HDL cholesterol than those whose parents did not (49.0 versus 51.7 mg/dl). Similarly, Feldman et al. [53] found that passive exposure of high school students to tobacco smoke as indicated by plasma cotinine levels was associated with a higher ratio of total cholesterol to HDL cholesterol and with lower HDL concentration and that this difference was between about 7% and 9%. However, there was no association between lipid profiles and the reported smoking habits of parents, siblings and friends. Also, the blood samples analyzed were non-fasting (which alters lipid profiles) and the level of saturated fat in the children's diet was not determined, nor was the children's active smoking status. Moskowitz et al. [54] found that children exposed to passive smoking had significantly lower HDL levels than the non-exposed group, but they also had lower total cholesterol values with no difference in the LDL/HDL ratio. Zhu et al. [24] found no significant difference in total serum cholesterol, triglycerides or HDL cholesterol between rabbits fed a cholesterol-enriched diet with and without exposure to passive smoking.

In a recent study, Roberts et al. [25] report that exposure to ETS acutely increases LDL accumulation in vessel walls. The measurement of accumulation was indirect; normal and ETS-exposed rat plasma containing fluorescently labeled LDL was perfused through isolated segments of rat carotid arteries and the amount of retained fluorescence was assessed photometrically for the whole wall. The results were somewhat variable and there was an associated change in lumen volume. The site of the retained fluorescence was not determined but did appear to be within the wall. The mechanism by which this might occur is not clear, although a recent study [55] reports that ETS leads to increased susceptibility of LDL to oxidation and to increased uptake of LDL by macrophages in a bioassay. The values recorded for individuals, however, were variable and the range within treatment groups were very broad. In vivo studies aimed at direct measurements of LDL accumulation in vessel wall cells after exposure to ETS are warranted.

We conclude that there is evidence that ETS causes an impairment of endothelium-dependent relaxation, possibly through impairment of NO release, but there is no evidence that this causes the development of atherosclerosis. We further conclude that there is no convincing biological evidence that exposure to ETS alters plasma lipid profiles but that alteration in the oxidation state of LDL could possibly increase uptake by vessel wall cells.

2.2. Acute effects on pre-existing disease

Little is known about particular sub-groups of people for whom the relationship between IHD and ETS may be different from that experienced by the general population. Some sub-groups may have a genetic predisposition to smoking-enhanced atherosclerosis. A recent study [56] documented the population distribution of an endothelial NO synthase polymorphism and identified an excess coronary risk, which is smoking-dependent, in patients with a particular genotype (ecNOS4a/a). Whether ETS increases the risk of these individuals for atherosclerosis, however, is not known.

Many studies have examined the effects of ETS on pathways and events associated with pre-existing IHD, notably thrombosis, exercise tolerance, arrhythmias, vessel wall reactivity and infarction. These aspects are discussed below.

Thrombotic pathway

A number of studies report that exposure to ETS increases the propensity for platelets to aggregate and decreases their sensitivity to anti-aggregatory prostaglandins [39, 57–59]. It is hypothesised that such changes increase the risk for thrombus formation but any increased risk will likely apply only to those with pre-existing disease, where rupture of plaques is a possibility. In general the data support claims of increased platelet activity in non-smokers exposed to cigarette smoke, both active and environmental. Smokers, on the other hand, are generally not responsive, showing overall decreased platelet sensitivity. There is, however, considerable variability both in the response of non-smoking individuals to smoke exposure and in baseline levels recorded for smokers and non-smokers.

Davis et al. [60] showed that passive smoking by ten healthy non-smoking men reduced the mean platelet aggregation ratio from 0.87 before exposure to 0.78 after exposure. The before values ranged from approximately 0.94 to 0.75 (estimated from their graph) and the after values from 0.89 to 0.64, with considerable variability occurring in the response by individuals. A wide variability is also seen in plasma concentrations of platelet factor 4 in habitual smokers as measured before (mean 13.6 ng/ml, range 6.8–39.2 ng/ml) and after smoking (mean 19.7 ng/ml, range 7.0–100 ng/ml) [59].

Burghuber et al. [58] measured the sensitivity of platelets to anti-aggregatory prostacyclin in smokers and non-smokers following both active and passive smoking. Smokers showed little change, but nonsmokers responded to both active and passive smoking with a significantly decreased index of sensitivity. Again, however, there was considerable variability in the indices, notably the before exposure values. The approximate mean values recorded for one group of smokers prior to active smoking was 0.35; the mean value noted for another group of smokers prior to exposure to ETS was 0.51. For non-smokers the respective values observed for two separate groups were 0.65 and 0.80. Following active smoking and exposure to ETS the indices noted for the non-smokers decreased by 0.17 and 0.25, respectively. Thus, although both groups experienced a decrease, the mean differences due to ETS exposure are not very different from the range of normal variability found across groups prior to exposure.

The biological significance of the variability in these parameters of platelet function is not clear. The argument for a significant effect of ETS on coronary heart disease needs to invoke a change from baseline values for each individual rather than an absolute change in platelet activity. Smokers show very little change, if any, following smoking or exposure to ETS [54] but are known to be at increased risk of thrombosis. It should be noted that the effect of ETS on the prostacyclin index for non-smokers is acute, with a decrease in the index being detectable within 15 min [59]; recovery to normal values is also rapid and occurs within a few hours. Animal studies similarly show an effect on platelet activity, with decreased bleeding times following exposure to ETS [24, 61], but again, the response is variable.

The components of ETS that alter platelet activity are not known but may act to inhibit platelet-activating factor acetylhydrolase and thereby increase the amount of platelet-activating factor. Miyaura et al. [62] have found that cigarette smoke extract significantly reduces acetylhydrolase activity in human plasma. Whether ETS has such an effect in vivo is not known. Nicotine is probably not the active component [63]. Indeed, a recent study found that transdermal nicotine significantly lowered plasma fibrinogen without affecting markers of platelet activation, indicating that nicotine may act to reduce cardiovascular risk [64].

Finally, a recent study by He et al. [20], referred to earlier in this review, indicates that exposure to high levels of ETS may correlate with severe atherosclerosis. Increased risk of thrombosis through exposure to ETS may be an important factor, but this has yet to be determined.

We conclude that ETS may increase the risk of thrombosis in those patients with cardiovascular disease since parameters of platelet function are adversely affected. Effects on individuals, however, are highly variable.

Hypoxia and exercise

There is evidence that ETS, or components of ETS such as carbon monoxide (CO), significantly increases ischemic stress in persons with pre-existing IHD [55, 65–68]. The effects, however, are generally small, often on the order of 10% or less. Healthy persons are either not affected [65] or only marginally affected [69].

Allred et al. [67] investigated the effect of CO exposure, sufficient to raise carboxyhaemoglobin levels to 2% and 4%, on exercise performance of men with IHD. Outcomes measured were ST-segment changes and time to onset of angina. At 2% carboxyhaemoglobin levels there was a 5% and 4% decrease in these outcomes, respectively, and at 4% carboxyhaemoglobin there was a 12% and 7% change, respectively. McMurray et al. [69] found a significant effect of passive smoking on exercise performance in young, moderately active women, but the differences as shown in Fig. 1 and 3 of their paper were very small. Moskowitz et al. [54] measured 2–3 diphosphoglycerate (DPG) levels as a marker for oxygen stress in children exposed to passive smoke and found a small increase averaging about 6%.

Other investigators have measured effects of ETS and CO on myocardial function. Gvozdjakova et al. [70] reported a significant decrease in respiration and phosphorylation rate in rabbit myocardial mitochondria with ETS exposure sufficient to raise carboxyhaemoglobin levels to about 6%, a level achieved in active smoking. Several studies report that CO causes myocardial dam-

age as assessed morphologically [71–73]. Damage occurred at high levels of CO exposure (200–300 ppm), but not in all animals, and there was no change at 50 ppm. There was also evidence of recovery over 48 h from damage induced by 180 ppm [72]. It should be noted that levels of CO in public smoking rooms has been reported as ranging from 5 to 50 ppm [24].

Interestingly, at the cellular level there is recent evidence that vascular smooth muscle cells may be capable of compensating for hypoxia through their own production of CO. In response to hypoxia, SMC and endothelial cells in coculture produce CO, which inhibits both cell growth and the production of vasoconstrictors [74].

We conclude that there is evidence for reduced exercise tolerance in persons with pre-existing disease exposed to ETS, but the effects are small and variable. In healthy persons exposed to ETS the effects are negligible.

Arrhythmias

Sheps et al. [75] investigated the frequency of single and multiple ventricular depolarisations (VDPs) in IHD patients exposed to CO levels sufficient to raise their carboxyhaemoglobin levels to 4% and 6%. Exercise induced an increase in VDPs at 6%, but not at 4%; recovery was rapid, occurring within 2 h. Leone et al. [76] reported in an abstract that six of ten patients with a previous myocardial infarction showed an increased number of extrasystoles when subjected to passive smoke during exercise. There is insufficient information, however, to critically review these data.

Przyklenk [77] has reported that nicotine adversely affects contraction of the myocardium in dogs following ischemia induced by coronary artery occlusion. There was no effect of nicotine prior to occlusion, implying that exposure to nicotine following an ischemic episode may worsen the recovery of myocardium. The author extrapolates the findings to passive smoking but presents no evidence to support this argument.

We conclude that there is evidence that the frequency of exercise-induced arrhythmias may be increased in IHD patients with elevated carboxyhaemoglobin levels. However, the level of carboxyhaemoglobin necessary for this to occur is unlikely to be achieved by exposure to ETS.

Artery wall reactivity

Quillen et al. [78] provide some clues as to the mechanisms whereby smoking could cause adverse effects on those with pre-existing coronary atherosclerosis. Coronary artery flow velocity in 24 long-term smokers was assessed with a Doppler catheter before and at 5 min after smoking 10–15 mm of one cigarette. The average diameter of the proximal and distal epicardial coronary arteries decreased to a small but significant extent, whereas in 2 of the 24 patients there was marked focal vasoconstriction. Coronary blood flow decreased by an average of 7% and coronary vascular resistance by 21%. In all the cases coronary diameter returned to baseline by 30 min after smoking. These authors concluded that active smoking caused immediate constriction of the proximal and epicardial coronary arteries in spite of increased oxygen demand by the myocardium and that, in patients with IHD, smoking of just one cigarette could produce myocardial perfusion abnormalities. They suggest several possible mechanisms whereby this vasoconstriction occurs, including activation of the sympathetic nervous system, circulating or locally released catecholamines or pre-existing dysfunction of the endothelium. The authors stress that all the patients in the study were long-term smokers and that the results cannot be extrapolated to ETS-exposed non-smokers.

Kool et al. [79] found that habitual smokers and non-smokers were not significantly different with regard to blood pressure, cardiac function, vascular resistance and vessel wall properties of large arteries, although the heart rate was 14% higher in habitual smokers. Smoking of one cigarette by habitual smokers caused short-term increases in heart rate, blood pressure and arterial stiffness. Two coefficients of stiffness were calculated that were dependent on both changes in vessel diameter and changes in blood pressure. Smoking resulted in no change in vessel diameter; thus, the change in stiffness was due to changes in blood pressure alone. The authors suggest that this increase in stiffness might increase the risk of plaque rupture with subsequent ischaemic events in persons with pre-existing CHD. The effect of smoking was not measured in non-smokers and it is not possible to extrapolate the results to ETS exposure.

We conclude that more direct studies of ETS exposure in non-smokers are needed to assess whether artery wall reactivity is a relevant pathway. Current data indicate that any such effect is likely to be transient.

Infarction

Two studies report that ETS increases the size of myocardial infarctions [61, 80]. The latter study (an abstract) reports a doubling of infarct size, but no change in the area at risk, in dogs exposed to ETS for 1 h/day for 10 days and then subjected to ligation of the circumflex artery. Zhu et al. [61] similarly report an almost doubling of infarct size in rats exposed to ETS for 3 days, 3 weeks, and 6 weeks. The exposure regime of four cigarettes/15 min for 6 h/day raised carboxyhaemoglobin levels to 8%. CO and air nicotine levels in the exposure chambers were 92 ppm and 1103 $\mu g/m^3$, respectively. As compared with the control group, infarct size in the ETS-exposed group nearly doubled at 6 weeks (34% versus 61%), with an increase from 34% to 43% being

seen at 3 weeks. At 3 days the values were 35% and 37%, respectively.

A significant exposure-response relationship is claimed; this is taken by Glantz and Parmley [11] as providing evidence that there is no threshold effect. Examination of the data in their Table 2, however, indicates that this conclusion may be inappropriate.

Infarct sizes at 3 days are similar in the control and exposed groups (15% versus 17%), as are the risk areas (43% versus 45%); thus, infarct sizes relative to risk areas are also similar. At 3 weeks the infarct sizes remain the same (16% versus 17%) but the risk area in the exposed group (39%) is less than the control value (44%). As a result the infarct size relative to the risk area is greater in the exposed group. In reality, however, the situation is not worse in the ETS-exposed group as claimed; the overall area affected by ligation (risk area plus infarct area) is actually smaller in this group than in the control group. Even if the assumption is made that the risk areas of 39% and 44% are effectively the same and that the infarct sizes of 16% and 17% are also the same, then, at best, there is no effect of passive smoking on the infarct size after 3 weeks of exposure. At 6 weeks there is an increase in infarct size but no increase in risk area. Overall the results are consistent with a threshold effect, an important consideration, given the high exposure regime that produced carboxyhaemoglobin levels equivalent to active smoking rather than ETS exposure.

The mechanism leading to increased infarct size is not clear, but ETS may worsen reperfusion injury through the activity of free radicals. Van Jaarsveld et al. [81] have shown that supplementation with the anti-oxidants alpha tocopherol and beta carotene can ameliorate experimental ischemic damage in isolated hearts taken from rats exposed to ETS.

We conclude that exposure to ETS may increase infarct size, but only with a strong threshold exposure effect.

3. Epidemiological criteria

3.1. Outcome of epidemiological evaluations

It is well accepted that there is a very large number of plausible risk factors for IHD that may act independently or interact with ETS. Any specific contribution of ETS is not yet well established, and it is not possible using the biological data to estimate the relative contribution, if any, of ETS to the multifactorial biological process of lesion initiation and development.

In assessing any such contribution, one needs to be guided by the relative risk (RR) obtained through epidemiological studies. On the basis of comprehensive searches of the literature we have managed to locate 25 such studies [82–106] (6 of them unpublished in the formal literature) at the end of 1997, reporting on the relationship between exposure to ETS and IHD among non-smoking adults, which we believe to be relevant. A short summary of the studies is provided in Table 1. Covariates considered in individual study analyses are listed in Table 2.

Of the studies considered, 15 are case-control or cross-sectional studies conducted in Australia, England, Scotland, China, Italy, New Zealand and the United States and 10 are prospective or cohort studies conducted in the United States, Scotland and Japan. The predominant measure of ETS exposure is through spousal smoking (Table 3), although 11 studies [83, 89, 90, 95, 96, 99, 101–105] consider other sources of exposure nine of them are indicated in Table 4. For two of the comparatively small United States studies [91, 92] and one cross-sectional study from Argentina [103] there was limited information available to us, and three of the studies [93, 96, 97] are recent unpublished theses. In what follows, we focus on the most recently published paper describing each study. For example, Hole et al. [85] update a report by Gillis et al. [106], Hirayama [88] updates his 1981 and 1984 results [107, 108]. Sandler et al. [86] update the findings of Helsing et al. [109], and Steenland et al. [89] apparently analyse one of the same data sets used by LeVois and Layard [102].

Consistency of reported estimates

Table 3 represents our best effort to give consistent figures for the studies listed in Table 1. Where they exist, we have used RR estimates for IHD associated with exposure to spousal smoking, adjusted for various factors listed in Table 1. (Other covariates and risk factors may have been considered in the various studies, but the reported analyses did not include them.) Where possible, corresponding two-sided 95% confidence intervals are also cited. In the remainder of this paper a significance level of 5% is adopted unless stated otherwise.

The subjectivity inherent in the compilation of relevant individual study estimates has led to considerable variation in the published collations of estimates reported in the reviews listed above. We attempt here to reconcile the data across these various sources using, in each case, the recent NH&MRC review [6] as a baseline value. Unfortunately, comparison with estimates collated from the 19 "acceptable published studies" in the recent review by Law et al. [13] is not possible since the data set is not reported and it is not possible to reconstruct it from their Fig. 1.

Garland et al. [82]. The NH&MRC [6] cites an RR of 3.5 (0.9–13.6). This is a crude RR (unadjusted for any covariate or other risk factor) for a population of ex-smokers and current smokers. Other cited figures are 2.9 (crude RR for current only) and 2.7 (cited by Wells [15], arguing that 2.7 = log(14.9), where 14.9 was (presumably mis-)stated by Garland et al. as the appropriate

Table 1 Characteristics of studies reporting on the association between exposure to ETS and heart disease in non-smoking adults (*AHSMOG* American air pollution survey, *ACS* American Cancer Society, *CPS-I* Cancer Prevention Study I, *CPS-II* Cancer Prevention Study II; *NMFS* National Mortality Followback Survey)

First author	Study period	Population	Study size	Covariates[a]
Cohort studies:				
Garland [82]	1963, for 10 years	Retirement community, California, USA	695 F entered, 2 unexposed cases	a,v,b,x,
Svendsen [83]	1973; average 7 years	18 cities in USA	1,245 M entered, 8 unexposed cases	a,b,n,g,e,v
Butler [84]	1976–1982	Seventh-Day Adventists, California, USA	11,060 spouse-pairs, 6,467 AHSMOG subjects; 20 unexposed cases	a
Hole [85]	Screened 1972–1976; average 11.5 years	Renfrew and Paisley, Scotland	671 M, 1,784 F entered, 30 unexposed cases	a,k,q,x,b,v
Sandler [86]	1963, for 12 years	Maryland, USA	4,162 M, 14,873 F entered, 437 F, 248 M unexposed cases	a,z,p,e
Humble [87]	1960, for 20 years	Georgia, USA	513 F entered, approx. 27 unexposed cases	a,x,b,v
Hirayama [88]	1966–1981	29 Districts in Japan	91,540 F entered, 118 unexposed cases	a,y
Le Vois [102]	1959–1960, for 13 years	ACS CPS-I, CPS-II, USA	CPS-I: entered 88,458 M, 267,412 F; 6,954 M, 2,217 F unexposed cases CPS-II: entered 108,772 M, 226,067 F; 1,566 M, 376 F unexposed cases	a,o
Steenland [89]	1982–1989	ACS CPS-II, USA	Entered 309,599 spousal ETS pairs; 2,049 M, 525 F unexposed cases	a,r,m,d,w,i,e, b,l,f,g,t,j,ϕ
Kawachi [105]	Established 1976; follow-up 1982–1992	Nurses Health Study, USA	121,700 F entered 1976; 32,046 never-smokers in 1982; 14 non-fatal and 3 fatal unexposed cases	a,g,i,m,d,v,ϕ, j,r,l,ρ,ζ
Case-control studies:				
Lee [90]	1979–1982	10 Regions in England	M: 41 cases, 133 controls; F: 77 cases, 318 controls	a,p
Martin [91b]	Unknown	Utah, USA	9,172 spouse pairs, 7,115 never-smoking women, 23 F cases	None (see text)
Palmer [92b]	Unknown	USA	F: 336 cases, 799 controls	No details
Jackson [93b]	1986–1988	Auckland, New Zealand	M: 49 cases; 184 controls; F: 20 cases, 174 controls	a,q,r
He [94]	1985–1987	Xijing, China	F: 34 cases, [illegible] controls	s,c,j,g,t,v
Dobson [95]	1988–1989	NSW, Australia	M: 183 cases, 293 controls; F: 226 cases, 332 controls	a,e,r
Liew [96b]	1989	Perth, Australia	M: 363 cases, [illegible] controls; F: 123 cases, [illegible]8 controls	a,r,t,s,d
Sexton [97b]	1987–1989	Perth, Australia	M: 102 cases, 102 controls	Not clear; see text
La Vecchia [98]	1988–1989	Northern Italy	M: 69 cases; F: 44 cases; F&M: 225 controls	a,k,e,h,x,b,d, m,c,v
He [99]	1989–1992	Xi'an, China	F: 59 cases, 126 controls	a,m,c,b
Layard [100]	1986	NMFS, USA	M: 475 cases, 998 controls; F: 914 cases, 1,930 controls	a,o
Muscat [101]	1980–1990	4 Cities, USA	M: 68 cases, 108 controls; F: 46 cases, 50 controls	a,e,m
Ciruzzi [103]	1991–1994	Part of FRICAS study, 35 clinics in Argentina	M&F: 336 cases, 446 controls	a,k,c,i,d,m,e,ζ
Cross-sectional studies:				
He [20c]	1985–1993	Xi'an, China; combined 2 previous case control studies and new patients	M&F: 78 cases, 83 controls with suspected or clinically diagnosed coronary artery disease	a,i,m,c,v,γ

Table 1 (contd.)

Case-sectional studies:				
Tunstall-Pedoe [104]	1984–1986	Scottish Heart Health study (random sample from practitioner visits)	786 M, 1,492 F never-smokers, 15–16 unexposed cases, 99–129 unexposed cases for all CHD based on self-report or serum cotinine	a,z,v,b

[a] Covariates accounted for in relative risk estimates are given in Table 2 and/or Table 3; other covariates may have been considered in the study; see Table 8 for definitions of abbreviations
[b] Not published in refereed journal
[c] Study included here for completeness but subsequently ignored because the response is the number of stenotic arteries

Table 2 Abbreviations used for covariates considered in individual study analyses

Symbol	Covariate	Symbol	Covariate	Symbol	Covariate
a	Age	l	Aspirin use	v	Cholesterol[a]
b	Blood pressure[a]	m	Hypertension	w	Arthritis
c	Family IHD history[a]	n	Weight	x	Obesity
d	Diabetes	o	Race	y	Husband's occupation
e	Education	p	Current marital status	z	Housing
f	Diuretic use	q	Social status	α	Residence
g	Alcohol	r	History of IHD	β	Work ETS
h	Coffee	s	Family history of hypertension	γ	Type A personality
i	Body mass index			δ	Spouse ETS
j	Exercise	t	Occupation/ employment status	ε	Employment status
k	Sex	u	4 CVD risk factors	ϕ	Estrogen use/ menopause (F)
ρ	Diet	ζ	Other factors[a]		

[a] Blood pressure systolic, diastolic, baseline or unstated. Family IHD history includes CHD (coronary heart disease), AMI (acute myocardial infarction) and CVD (cardiovascular disease). Housing includes type, quality or tenure. Cholesterol includes cholesterolemia, high-density lipoprotein cholesterol, total cholesterol and hyperlipidemia. Other factors included by Kawachi et al. [105] are past use of oral contraceptives, vitamin E intake, saturated fat and the father's occupation when the subject was aged 16 years

adjusted RR); we adopt the latter. This study is based on a very small number of unexposed cases and should thus be afforded little weight in any overall evaluation, regardless of the estimate used.

Svendsen et al. [83]. The NH&MRC [6] cites an RR of 1.61 (0.96–2.71), which is that given by the author for fatal plus non-fatal events. The reported RR for fatal events is 2.23 (0.7–6.9). This study used a high-risk group and should be included in any overall evaluation with caution.

Helsing et al. [109]/Sandler et al. [86]. The NH&MRC [6] cites an RR of 1.31 (1.1–1.6) for males and 1.24 (1.1–1.4) for females, taken from Helsing et al. [109], whereas Sandler et al. [86] report an RR of 1.31 for males but 1.19 (1.04–1.36) for females as based on the same number of deaths and using the same confounding factors. This discrepancy was noted by Lee [110], who conjectures that it may be due to different statistical methods of adjustment.

Butler [84]. This unpublished study is omitted by the NH&MRC [6] and by Law et al. [13]. It reports an adjusted RR for mortality of 1.05 (ex- plus current smokers) and a crude RR of 1.4 (current smokers). Estimates of 1.29 for females and 0.54 for males are cited by Glantz and Parmley [11] and Wells [15].

Hole et al. [85]. The NH&MRC [6] cites an RR of 2.01 (1.2–3.3) for males and females combined, which is similar to that mentioned by Glantz and Parmley [10] and is taken from the authors' Table VII. However, Glantz and Parmley [11] and Wells [15] cite 1.65 (0.79–3.46) for females and 1.73 (1.01–2.96) for males, reportedly on the basis of a private communication to Wells from Hole in 1990.

Hirayama [88]. The NH&MRC [6] cites an RR of 1.30 (1.06–1.60), which is slightly revised from this author's earlier figures [107, 108], but Glantz and Parmley [11] and Wells [15] cite 1.15 (0.93–1.42), which is perhaps a weighted average of the age-adjusted RR estimates given by Hirayama [88].

Steenland et al. [89]. This most recently published analysis of a very large cohort study (American Cancer Society CPS-II) asserts to be an analysis of one of the same data sets analysed by LeVois and Layard [102] as part of a larger assessment of publication bias and was cited by Gori [12]. LeVois and Layard [102] also analysed the CPS-I study; no significant RR or exposure-

Table 3 Reported and overall estimates of RR (95% CI) for IHD in adults associated with exposure to spousal or household smoking

	Reference[b]	Mortality[a]		Morbidity[a]	
		Females	Males	Females	Males
Cohort studies:					
Garland [82]	See text	2.7 (0.70, 10.5)			
Svendsen [83]	T8		2.23 (0.72, 6.92)		1.61 (0.96, 2.71)
Butler [84]	Abstract	1.40 (0.51, 3.84)			
Hole [85]	See text	1.65 (0.79, 3.46)	1.73 (1.01, 2.96)	1.13 (0.69, 1.86)	
Sandler [86]	T5	1.19 (1.04, 1.36)	1.31 (1.05, 1.64)		
Humble [87]	T3	1.59 (0.99, 2.57)			
Hirayama [88]	T2, see text	1.15 (0.93, 1.42)			
Steenland [89]	T2	1.10 (0.96, 1.27)	1.22 (1.07, 1.40)		
Kawachi [105]	Text[c]			1.54 (0.88–2.70)	
Case-control studies:					
Lee [90]	See text			0.93 (0.54, 1.62)	1.24 (0.59, 2.59)
Martin [91]	Abstract			2.6 (1.2, 5.7)	
Palmer [92]	Abstract			1.2	
Jackson [93]	Abstract	5.8 (0.95, 35.2)	1.1 (0.23, 5.20)	2.70 (0.57, 12.3)	1.03 (0.27, 3.90)
He [94]	He (1994)			1.50 (1.28, 1.77)	
Dobson [95]	T2			2.46 (1.47, 4.13)	0.97 (0.50, 1.86)
Liew [96]	T13.4			1.50 (0.50, 4.49)	1.27 (0.39, 4.10)
Sexton [97]	T51		9.95 (2.25, 44)		6.36 (1.2, 33.6)
Vecchia [98]				1.20 (0.60, 2.50)	(combined M/F)
He [99]	p382			1.24 (0.56, 2.72)	
Layard [100]		0.99 (0.84, 1.16)	0.97 (0.73, 1.28)		
Muscat [101]				1.5 (0.9, 2.6)	(combined M/F)
Ciruzzi [103]	Abstract			1.43 (0.9–2.0)	(combined M/F)
Meta-analysis [d]					
Overall analysis		1.24 (1.09–1.41)		1.47 (1.31–1.65)	
Exclude possible outliers		1.18 (1.07–1.31)		1.46 (1.30–1.64)	
Excluding ex-smokers		1.32 (1.10–1.59)		1.47 (1.30–1.65)	
Replace Steenland [89] with Le Vois [102]		1.24 (1.08–1.43)			
Combined outcomes			1.35 (1.14–1.60)		

[a] Mortality defined variously as death from IHD, atherosclerotic heart disease, cardiovascular (CV) heart disease, all CV deaths. Morbidity defined variously as morbidity, non-fatal myocardial infarction (MI) or coronary artery disease, non-fatal MI, and fatal and non-fatal acute myocardial infarction

[b] Unless otherwise stated, reference is to the original paper (*T* Table)

[c] Kawachi reports 1.19 (0.63–2.23) for occasional exposure, 2.11 (1.03–4.33) for regular exposure; the figure cited in Table 2 is a weighted average using a logit approximation to the variance

[d] Possible outliers are Liew [96], Sexton [97] and Jackson [93]. Studies with suspected or confirmed ex-smokers are those of Steenland [89] and Muscat [101]

response relationship was found. When both CPS studies are combined, the overall RRs for mortality were 1.02 (0.98–1.07) for females and 0.97 (0.91–1.03) for males. Steenland et al. [89] assert that the reason for the difference between their (higher) RR estimates and those of LeVois and Layard [102] is, in part, that the latter included subjects exposed to former as well as currently smoking spouses and used less accurate data. Without access to the data we cannot comment on this, but the debate, continued in a series of correspondence [111–113], highlights the difficulty of agreeing on the relevant data set and consequent estimates even within the same study. Because of this debate we have omitted LeVois and Layard [102] from Tables 3 and 5; we note later the difference that this makes in an overall meta-analysis.

He et al. [99]. The NH&MRC [6] cites an RR of 1.24 (0.56–2.72), which is an adjusted estimate for exposure to spousal smoking. An adjusted RR of 2.89 (1.13–7.34) is cited by Glantz and Parmley [11] and Wells [15]. The reference for this latter figure is not the 1994 paper but a 1993 conference abstract; moreover, Glantz and Parmley [11] appear to plot a more moderate estimate in their Fig. 3.

Lee et al. [90]. The NH&MRC [6] cites RRs adjusted for age and marital status without confidence intervals as reported in this paper. Wells [15] gives confidence intervals for the RR estimates, adjusted for both of these variables, and we cite these in Table 3.

Jackson [93]. This unpublished study is cited only by Glantz and Parmley [11] and Wells [15]. The very wide confidence intervals shown in Table 3 illustrate the extremely small numbers on which the estimated RRs are based.

Layard [100]. This recently published case-control study finds an adjusted RR for mortality of 0.97 (0.73–

Table 4 Reported estimates of RR (95% CI) for IHD in adults associated with exposure to ETS from sources other than spouse or household

Author	Ref.[b]	Outcome[a]	Exposure	Gender	RR (95% CI)
Cohort studies:					
Svendsen [83]	T8	Morbidity	Both spouse and co-workers	M	1.7 (0.8, 3.6)
			Co-workers, not spouse		1.0 (0.5, 1.9)
		Mortality	Co-workers		2.6 (0.5, 12.7)
Steenland [89]	T4	Mortality	Currently exposed at work	M	1.03 (0.89, 1.19)
				F	1.06 (0.84, 1.34)
				M < 65 yr	1.10 (0.92, 1.31)
				F < 65 yr	1.09 (0.78, 1.52)
			Currently exposed elsewhere (not home or work)	M	1.03 (0.93, 1.13)
				F	0.91 (0.83, 1.00)
				M < 65 yr	1.7 (0.90, 1.27)
				F < 65 yr	1.13 (0.90, 1.42)
Kawachi [105]	Text	Morbidity (multivariate analyses)	Home or work		
			Occasional exposure	F	1.58 (0.93, 2.68)
			Regular exposure	F	1.91 (1.11, 3.28)
Case-control studies:					
Lee [90]	T5	Morbidity	Combined index (home, work, travel, leisure)		
			score 2–4	M	0.43 (0.2, 0.9)
				F	0.59 (0.2, 1.1)
				M/F	1.24
			score 5–12	M	0.43 (0.1, 1.4)
				F	0.81 (0.2, 2.0)
				M/F	1.93
Dobson [95]	T4	Morbidity	Work	M	0.95 (0.51, 1.78)
				F	0.66 (0.17, 2.62)
Liew [96]	T13.6	Morbidity	Workplace	M	4.26 (1.22, 14.9)
He [99]		Morbidity	Work	F	1.9 (0.9, 4.0)
			Any		2.4 (1.0, 5.6)
Muscat [101]		Morbidity	Current workplace:	M	1.2 (0.6, 2.2)
			Inside passenger vehicles:	F	1.0 (0.4, 2.5)
				M	"No difference"
				F	2.6 (0.9, 8.0)
Tunstall-Pedoe [104]	T3[c]	Morbidity	Exposed in the last 40 h	M,F	1.89 (1.23–2.89)

[a, b] See footnotes to Table 2

[c] The estimate for Tunstall-Pedoe is a variance-weighted average of odds ratios given for diagnosed heart disease based on serum cotinine

1.28) for males and 0.99 (0.84–1.16) for females. It has been cited by Gori [12] and Glantz and Parmley [114]; the latter criticise Layard for including subjects exposed to former smokers.

He et al. [20]. This study, discussed in section 2.1, is referenced only in the NHMRC report [6]; it combines new subjects with those included in two previous case-control studies and finds a statistically significant dose-response relationship with spousal exposure and number of stenotic arteries. As in the NHMRC report [6], we include this last study in our Table 1 for completeness but thenceforth ignore it because its response (stenotic arteries) is not consistent with that of the other studies.

Kawachi et al. [105]. Results from this newly published study of United States nurses are included without critical evaluation in the review by Law et al. [13]. In the following section we discuss aspects of study design, particularly selection bias, some of which have been debated in the literature [116–120] and which lead to doubt about the validity of estimates from this study.

Tunstall-Pedoe et al. [104]. This cross-sectional study is referenced by Law et al. [13] and by the NHMRC report [6]. The NHMRC report details results relating to comparison between serum cotinine and self-reporting but does not include the study in the summary tables for RR (Tables 6.2, 6.3). Results are given for various types of heart disease, including questionnaire angina, undiagnosed CHD and diagnosed CHD.

Other studies. Martin et al. [91] do not give any confidence intervals for the reported adjusted RRs; in Table 3 we cite the RR and confidence interval given by Wells [15]. Details of confounders for Sexton [97] are taken from his Table 51 and those for He et al. [94], from Lee [110]. Ciruzzi et al. [103] provide only an abstract, which is referenced by and included in the

meta-analysis of Law et al. [13] but is ignored in the NHMRC report [6].

The above discussion indicates the extreme difficulty of trying to find appropriate numbers on which to base any judgement, and all of what follows must be seen in this light.

Overall conclusions

On the basis of the evaluations to follow, we form the following conclusions:

Test 3 (*strength of association*): we conclude that the reported relative risks are significantly raised. They are, however, not strong enough to pass this test at the level required for causality.

Test 4 (*biological gradient*): we conclude that there is limited support for a biological gradient in the studies published to date.

Test 5 (*consistency of association*): we conclude that although the reported relative risks are generally raised (an observation already largely taken into account in the evaluation of test 3), the effect is not consistent in the sense of this criterion.

Test 6 (*specificity of association*): we conclude that there is no demonstrated specificity of magnitude, no demonstrated specificity of exposure, and no demonstrated specificity of response. In this case, some of the alternative explanations for increased RR of IHD are such that, unless they are demonstrated to have null effect, they could account for much of the observed increase in relative risk.

3.2. Strength of association

There are several issues that must be considered in assessing strength of association. These are:

(a) Initial evaluation: is there a prima facie case based on epidemiological studies that leads us to believe the association might be strong?
(b) Statistical significance: is the observed strong association due to chance?
(c) Confounders: is the observed strong association due to the exposure or is it possibly caused by other variables?
(e) Bias: is the observed strength a true representation of the overall picture or is there bias due to the studies or data being chosen selectively, or for any other reason?

Some of these, especially the evaluation of statistical significance and removal of confounders, are clearly critical steps in establishing causality; indeed, although they are not in the original set of criteria of Hill [7], they are considered by others such as Rothman [120] and Tweedie and Mengersen (in preparation) to be separate criteria. Here, however, we have chosen to work within the Hill framework; thus we include them at this point.

Initial evaluation of strength

The strength of a study in this context is usually measured by the RR of IHD in the population exposed to ETS. It is often asserted in the literature that for any

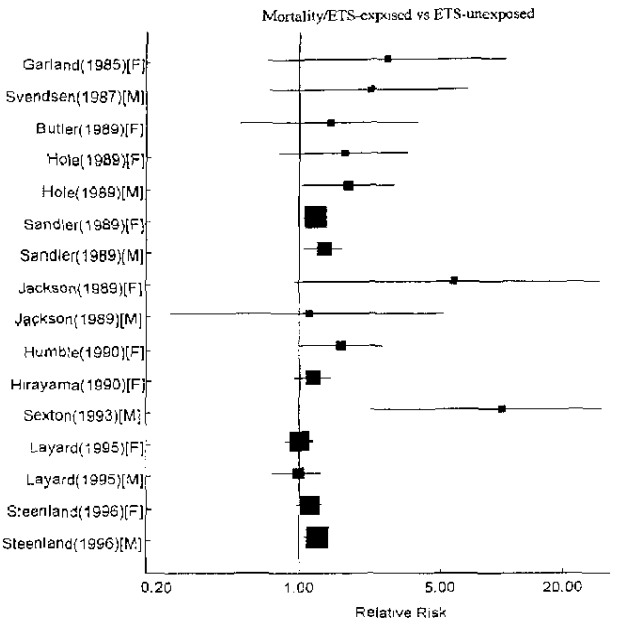

Fig. 1 Comparison of RR (and 95% CI) for individual studies of mortality from IHD associated with exposure to ETS

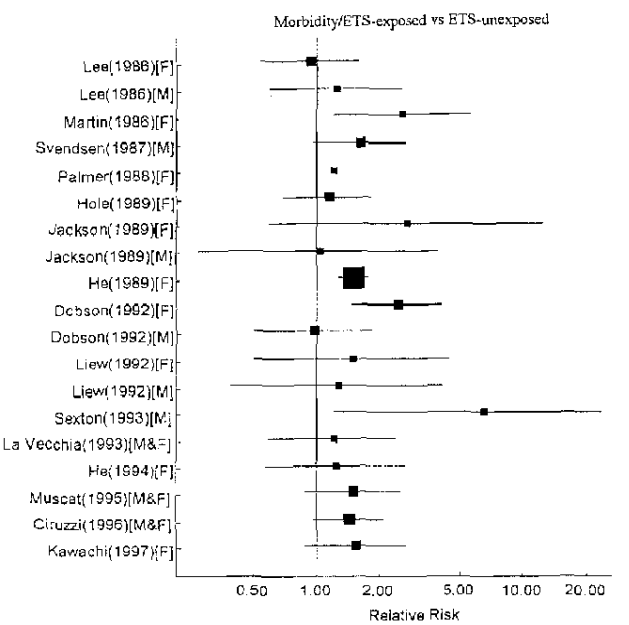

Fig. 2 Comparison of RR (and 95% CI) for individual studies of morbidity from IHD associated with exposure to ETS

single study an RR of at least 2 is required before the conclusion that a relative risk estimate can be considered strong and, in particular, to be free of the influence of confounders and other sources of bias and selectivity. Cornfield is quoted by Wynder [121] as suggesting that even an RR under 3 might be considered weak. Mantel [122] advocates that values below 2 should not be regarded as established. Layard [123] states that "relative risks of less than 2 are generally considered to be weak". Doll [124] even states that "past experience suggests that confounding is seldom likely to be the explanation if the lower 95% confidence limit of the estimated RR is greater than 3", and the United States EPA rejected causality of EMF for lung cancer partly due to the RR being below 3.0.

In Table 3, only 8 of the 35 RRs reported for either mortality or morbidity exceed 2.0, and 6 of these have very large confidence intervals indicative of small underlying data sets. Figures 1 and 2 provide a visual impression of the size and variability of the individual estimates of RR for mortality and morbidity, respectively, reported in this table.

Although Table 3 focuses on spousal exposure to ETS, consideration of other sources of exposure also fails to bolster the case for strength of association as indicated in Table 4. Of the nine studies listed, only four report a significantly increased RR, and then only in some populations. Of these, Liew's [96] estimate is over 3 times that reported by him for exposure to spousal smoking, Kawachi et al.'s [105] various estimates appear to give an inconsistent dose-response picture, and Tunstall-Pedoe et al.'s [104] results vary considerably between self-report and serum cotinine. Moreover, three studies [89, 90, 95] report some RR estimates that are less than unity, although apart from some sub-groups in Lee et al.'s [90] study, these are not statistically significantly lowered.

Statistical significance and combined analysis

For RR estimates that are not statistically significantly increased, there remains an unsatisfactorily large probability that an even an observed "strong" relative risk may be due to chance fluctuation or irrelevant "background causes" within an individual study.

As indicated in Tables 1 and 3, although many of the studies of spousal smoking have a large number of enrolled subjects, the number of cases may be quite small; hence, although there are only nine statistically significant estimates in Table 3, this may be due to the lack of power in the individual results. It may be possible to obtain a better overall picture of the strength of association through meta-analysis, that is, by "borrowing strength" from the body of studies (see, for example, Cooper and Hedges [125] and many other papers on this topic).

There are, however, concerns about study quality and comparability that compel careful consideration of the validity of combining such studies at all. As well as recognised differences in population groups, periods of study and study design, we identify the following further difficulties in combining them:

1. The studies do not measure the same outcome or exposure. Death and non-fatal events are both considered and the latter is variously defined. Exposure may be from the spouse, home, work or various combinations of these, for different periods of time and at different stages of the study. Consequently, a meta-analysis may be uninterpretable if there is a true difference in RR between the various measures.
2. The study populations are not comparable. Not only may they not be representative of the population from which they are drawn, but there may be strong between-study differences in populations. In the study of lung cancer, it has been observed that different RRs may apply to different countries or genders [126, 127]. Moreover, different age structures between studies may be a strong covariate and, for example, the relatively young and healthy population studied by Kawachi et al. [105] has raised considerable comment. If one wishes to apply results to a particular population, it is not strictly valid to combine studies other than those measuring comparable associations in equivalent populations.
3. The relative risk has not been established to be constant over time. There is substantial literature that asserts that mortality from heart disease is variable; for example, it is decreasing in Australia but the reasons for this are not yet well understood [92, 128]. If other risk factors or patterns of exposure have also changed, a summary RR estimate over all time periods may be invalid or inapplicable [129].
4. Statistical methods differ substantially. A variety of methods of estimating RR has been used in the individual papers; Mengersen et al. [127] illustrate that this may result in quite different individual and overall estimates when RRs are close to unity and, in some cases, may change the resultant inferences. This is clearly exemplified again in the formal meta-analyses below.
5. Confounding factors are not adequately controlled. This potentially serious problem for such a multifactorial disease is discussed below.
6. The results may be partially or entirely explained by misclassification and bias. The considerable body of data that shows that this problem is real is also discussed below.

Despite these caveats, a meta-analysis of apparently disparate studies may shed light on the source of the disparities. Such differences may perhaps be formally incorporated into the analysis via a random effects model, from either frequentist or Bayesian perspectives, in which additional error is incorporated to allow for individual study variation as well as the traditional between-study variation [128, 130, 131].

Although it rejects a formal meta-analysis, in assessing the impact of ETS on cardiovascular disease the NH&MRC report [6] considers 22 estimates of RR from individual studies and adopts an overall RR of about 1.3 based on previous meta-analyses or a median RR of 1.24 with quartiles given by 1.02 and 1.62 (p. 157). This is not dissimilar to the overall RR of 1.23 (95% CI 1.1–1.4) obtained by Wells [15] and cited by Glantz and Parmley [11], the "weak" overall association reported by Lee [110] (p. 188), and the overall RR of 1.30 (95% CI 1.22–1.38) at age 65 years reported by Law et al. [13].

We have carried out meta-analyses under a random effects model, and the results are appended to Table 2: these confirm that RRs of around 1.24 for mortality and 1.47 for morbidity are supported prior to consideration of other issues. The meta-analyses were based on the standard DerSimonian and Laird approximation to the between-study variance and were carried out using the combined male-female data within each study if these were provided separately. They are almost identical in this case to those arising from a model with an improved approximation [132] and a Bayesian hierarchical model.

Because of the inconsistency of reported RRs we have also conducted sensitivity analyses. First, we examined the impact of excluding the potential outlier results of Liew [96], Jackson [93] and Sexton [97] ; second, we excluded studies with supposed former smokers [88, 100] ; third, we replaced Steenland [89] by the lower combined CPS-I and CPS-II estimates reported by LeVois and Layard [102] ; and fourth, we combined mortality and morbidity results in a simplistic analysis (assuming independence between estimates) since some reviews [13, 15] do not distinguish between the two outcomes.

We also analysed males and females separately for both mortality and morbidity using a covariate analysis. Using mortality as an endpoint, males had a slightly higher RR of 1.31 with 95% CI (1.05, 1.63) than did females (RR = 1.15; 95% CI 1.03, 1.28); this was reversed for morbidity, with females having a slightly higher RR of 1.51 with 95% CI (1.23, 1.84) than did males (RR = 1.36; 95% CI 0.99, 1.89). However, in neither case was the interaction with sex found to be significant with this small number of studies, and the pooled estimate in Table 3 seems to be reasonable.

On the whole, these meta-analyses show that when estimates are pooled the resulting combined RR is formally statistically significantly raised at the 95% level. The sensitivity analyses in Table 3, however, demonstrate some lack of robustness in the meta-analysis results, particularly for mortality. This supports the concerns raised above about the reliability of any overall estimate, particularly in causality assessment or related estimation such as attributable risk.

Overall, although both the estimates and significance statements must be viewed with caution in light of the caveats outlined above, there is a prima facie case for strength of association. It is now important that other issues be considered in the evaluation of the strength of this association. Although there is no single rule against which to make such an assessment, Wynder [133] states that there may be cause for concern about the impact of poor study quality if the overall RR is less than 1.5, and other authorities use minimum rates of 2–3 as benchmarks as discussed above.

Below we consider some such possible explanations other than causal association with ETS, and we see particularly that publication and misclassification bias may account for much of the observed excess risk and significance levels.

Confounders and risk factors

The effect of confounders for such a multifactorial disease is potentially an influential source of bias and is clearly one of the major difficulties involved in trying to untangle causal relationships between ETS and IHD. In our opinion, consideration of the impact of confounders and other risk factors is two-fold:

(a) Is there any other risk factor for IHD that is sufficiently intimately linked with exposure to ETS that it could explain the observed association?
(b) Are there other factors that of themselves may not be causal but are sufficiently strong "confounders" that they influence the observed association?

It is extremely difficult to rule out the possibility of (a), given that there are over 200 suggested risk factors for heart disease [134]. These factors may be directly measurable (for example, blood pressure, cholesterol, obesity, previous history of IHD, alcohol intake) or indirectly inferred through a surrogate (for example, socioeconomic status, education, housing quality). Consideration of the entry criteria and adjustment factors used in each study indicate that control of possible major risk factors is sometimes poor and certainly inconsistent between studies. This concern is exemplified in the study by Kawachi et al. [105], in which the RRs adjusted for multiple risk factors are consistently smaller than the unadjusted estimates or those adjusted only for age.

Diet is one risk factor that has attracted attention. Its effect on the association between ETS and IHD has been identified in some individual studies [99, 116] and is supported by studies of other associations such as that between diet, ETS and lung cancer [135, 136]. A substantial difference in dietary habits among active smokers as compared with non-smokers has been reported [119, 137–140], and this plausibly extends to non-smokers with smoking spouses. Among non-smokers, RRs have been observed for IHD associated with various dietary factors that are at least as high as those observed with ETS exposure. If there is indeed a differential effect between those exposed and those unexposed, or between cases and controls, such a confounder must not be ignored in assessment of the ETS association.

Similarly, although He et al. [99] report a crude relative risk estimate of 2.12–2.45 (depending on the source), the values reported in their Table VI are substantially weaker (1.24 and 1.85, respectively) after adjusting for total and HDL cholesterol (among other factors).

Another important sub-population for which different relative risks may apply is subjects with previous IHD. Although the biological literature routinely differentiates between initiation and exacerbation, as discussed above in our review of these studies, only the epidemiological study of Dobson et al. [95] addresses previous IHD and finds it to be a significant confounder for smoking and the risk of heart attack or coronary death.

Heart disease at the baseline of a longitudinal study of mortality is also a (very direct) risk factor. Steenland et al. [89] report RRs of mortality for currently exposed subjects with no IHD at baseline of 1.18 (0.98–1.41) for males and 1.07 (0.90–1.26) for females. For subjects with IHD at baseline, corresponding RRs are noticeably larger, although not significantly different – 1.24 (1.01–1.53) for males and 1.14 (0.90–1.44) for females. Active exclusion of subjects with a past history of CHD, as in the study by Kawachi et al. [105], raises concern about selection bias [115] as discussed below.

In answer to (b), there is substantial variability in the identification and control of confounders such as age and gender both in the design and the analysis stages of the individual studies. As an example, it is well recognised that it is important to account for age. Roe (see Witorsch [141], p. 164) states that coronary heart disease is not a single disease but at least two; it is related to different factors in men less than 50 years old as compared with men older than 50 years. However, if adjustment for confounders are made, they must be appropriate. Again with respect to age, simple comparability of age groups between cases and controls may not be sufficient since discrepancies may still exist between exposed and unexposed groups, and surrogate comparisons may unfortunately not be valid. As an example of the latter, which has attracted discussion elsewhere, Hirayama [107] did not use accepted cohort analysis methods and standardised by age of spouse instead of age of subject; when this was remedied [88] the estimates were quite different, although Hirayama states that his conclusion about the strength of association remained the same. Law et al. [13] explicitly state that they account for age in their formal analysis, but details of their methodology are not provided.

Adjusting for bias

There is a number of sources of systematic bias in the set of studies of the association of ETS and IHD that need to be accounted for in assessment of overall strength of association. These are selection bias, publication bias, data dredging, subject misclassification bias, and bias due to ignoring of background exposure.

Selection bias

If the study population is not representative of the general population, it may not be possible to extrapolate observed results to the wider community, but, more problematically, it may not even be possible to compare cases and controls. This bias has been suggested as a plausible explanation for inconsistent results in the study by Kawachi et al. [105]. As part of a series of correspondence identifying deficiencies in this study's design, Adlkofer [115] argues that the reported high RR estimates may have been due to the exclusion of a large proportion of women with a history of CHD that "inevitably" resulted in a higher prevalence of undiagnosed CHD cases in the group of passive smokers. Kawachi's response [119] includes a reanalysis in which the adjusted relative risk of total CHD among regular passive smokers as compared with unexposed women was reduced from 1.91 (95% CI 1.11–3.28) to 1.73 (1.06–2.84) after inclusion of the 20 cases of CHD confirmed during follow-up.

Another argument based on selection bias is that the "unexposed" control group may be overly healthy and not representative of the normal population (a point also raised by Gori [118] and not covered in Kawachi's response [119]) and that the "exposed" group is in fact experiencing normal mortality rates rather than increased rates. This would explain the overall relative risks being raised so much more than has been seen in other studies, the seemingly low incidence rates in the control group and the more normal ones in the exposed group, the pattern of interim values that are used to justify the lack of effect of misclassification but are actually quite inexplicable under the ETS interpretation,

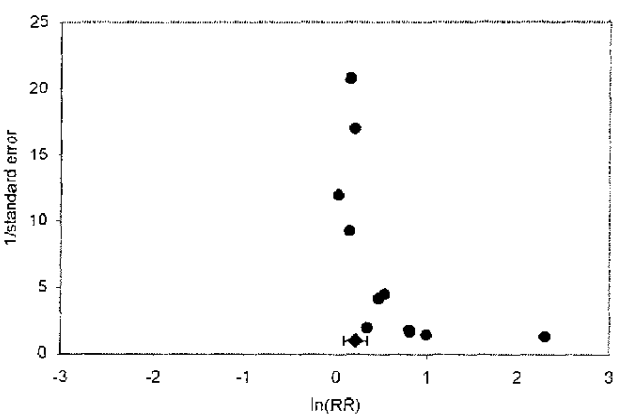

Fig. 3 Funnel plot of RR of mortality from IHD associated with exposure to ETS

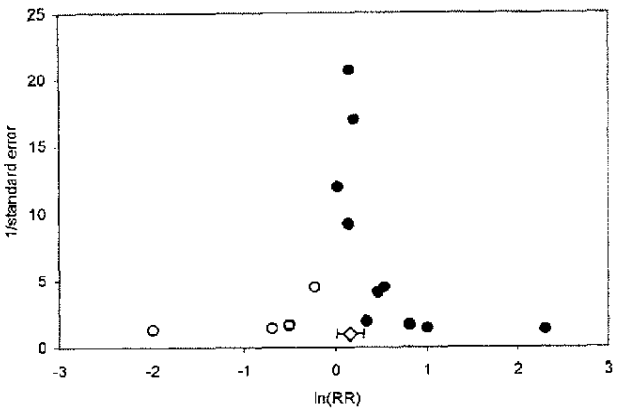

Fig. 4 Funnel plot of mortality data augmented by "filling" of five missing studies

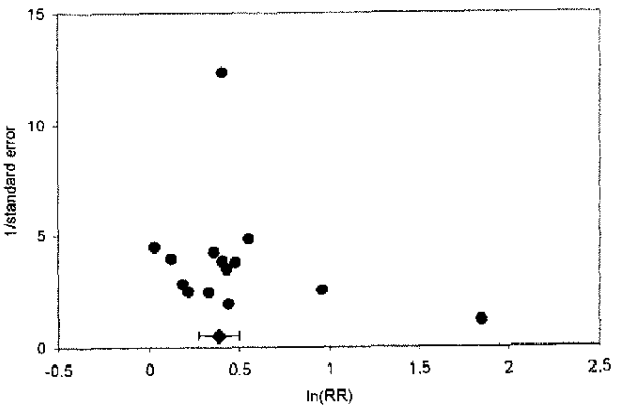

Fig. 5 Funnel plot of RR of morbidity data: estimates of the number of missing studies are 0–1

and the dose-reponse results, which even after adjusting for the control group still appear to be out of line with the rest of the paper.

Publication bias

A common problem in meta-analysis using literature reviews is distortion of the overall picture of an association through publication bias. Positive studies are more likely to be published than negative results [142]. Chalmers and Buyse [143] provide some indication of the level to which non-reporting of insignificant studies may bias overall assessment. Mengersen et al. [127] and Givens et al. [144] find clear support for this type of bias in the studies of ETS exposure and lung cancer.

There are insufficient data in the IHD studies to firmly establish the existence or impact of publication bias, but its detection in other ETS areas and the existence of unpublished studies [84, 91–93, 96, 97] of IHD raise the issue for debate [14, 102, 119]. Funnel plots of the mortality and morbidity data, given herein in Figs. 3 and 5, respectively, indicate the possible presence of publication bias in this data set. In these figures the ln(RR) is plotted against the study size, represented by the inverse standard error of the ln(RR). If no publication bias is present, symmetry should be observed in these plots.

As alternatives to the simplistic *P*-values approach taken by Law et al. [13], the methods of Givens et al. [144] and Duval and Tweedie [145] use more formal analyses to estimate the number of studies that appear to be "missing" and estimate the impact that this has on the overall relative risk. As based on the data in Table 3, the method of Duval and Tweedie [145] estimates around five to six unpublished studies of mortality but only zero to 1 missing study of morbidity. Figure 4 shows the effect of accounting for the missing mortality studies; the overall RR changed from 1.24 to 1.15 with 95% CI (0.996, 1.32) after accounting for publication bias. When males and females are considered separately, it appears that there may be four missing female studies and two missing male studies, and the above reduction in the relative risk seems to come more from the missing male studies than from the missing female studies. Missing studies, if any, in morbidity appear to make virtually no change in the relevant RRs.

Data dredging

The problem of data dredging (which exacerbates the possibility of publication bias) is well acknowledged but often difficult to assess on the basis on published papers. There are two issues that contribute to the problem: incorporation of results from a study in which an hypothesis is both generated and tested using the same data, and multiple testing in which data are subjected to many comparisons in the search for large or statistically significant results. Whereas hypothesis generation and multiple comparisons are useful exploratory tools, only results that apply to some pre-planned hypothesis should be considered as confirmatory.

Data dredging in the studies of IHD and ETS has several possible sources. Most of the analyses in the studies listed in Table 1 were based on sub-groups of more general studies. For at least three analyses [83, 88, 90], data on ETS and IHD were obtained only in the latter part of larger studies. Although this may be acceptable in large studies, such practice is strictly capable only of generating hypotheses or should be adjusted for the multiple comparisons involved.

In some individual studies, specific sub-groups are identified separately, with no biological or other rationale, or combined in ways that make the resultant RR difficult to interpret. For example, Garland et al. [82] present results recorded for ex-smokers and current smokers, then calculate a combined RR by merging the two exposure categories. This leads to an anomaly of most (15/17) deaths occurring in the

ex-smoker exposure category and provides (perhaps spuriously) more power for a combined RR estimate. Not only is the interpretation of this estimate difficult, given biological evidence of the difference between these two groups, but it may be an artefact of data dredging.

Data dredging may also be suspected if a paper focuses on ETS but this is actually only a peripheral part of the original study. For example, Kawachi et al. [105] ask a single (quite non-specific) question regarding ETS in the initial questionnaire of a 10-year study and undertake no follow-up on this exposure. It is difficult to accept that ETS was a major focus of this investigation or that this side study would have been published if the results had been negative. One can only speculate as to how many other major studies have information on ETS that has not yet been analysed (as was the situation with Kawachi et al. [105] until recently) or will never appear due to the lack of "interesting" results.

Misclassification

Misclassification of smoking status is an acknowledged problem in epidemiological studies of spousal ETS exposure. As developed for the association between ETS and lung cancer [110, 126, 147, 148], if supposed non-smokers are actually smokers, then the difference in marital patterns together with any higher RR for IHD and active smoking will systematically lead to overestimates of the RR for ETS.

This source of bias may not be as serious a factor in the assessment of IHD as it is for lung cancer since the RR for the "contaminating" misclassified group of active smokers, if it is around 1.7 [147] as is usually asserted, is not strong enough to provide substantial bias. Using a data-based sensitivity approach with a variety of published estimates of misclassification, marriage concordance, and active smoking RR, Tweedie et al. [147] have demonstrated that a RR of around 1.15 for IHD associated with ETS exposure may easily be observed even if the true RR is unity. This is in the order of many estimates actually reported for IHD. In general, we judge that this bias might account for an increase in the observed relative risk of around 0.05–0.10 unless steps have been taken to sharpen this aspect of study quality.

Dobson et al. [95] suggest that in their case-control study, cases may underreport smoking and, hence, reduce the magnitude of estimates of risk or may exaggerate smoking status as an explanation for the disease; thus, the observed risk could be spuriously raised or lowered. Conversely, Svendsen et al. [83] made careful measurements at baseline and follow-up to rule out misclassification of active smokers as non-smokers. They found no such differential misclassification. In the cohort studies of Hirayama [88], Sandler et al. [86] and Kawachi et al. [105] the smoking habits of both subjects and spouses were ascertained at the beginning of the study but were not updated during the study period; therefore, there is no information about the number of subjects or spouses who changed smoking habits during this period. He et al. [99] provide some information on retesting of 35 hospital subjects (16 cases and 19 controls) and report 75–95% agreement on 10 risk factor tests. Agreement on exposure was 74.3% (workplace) and 91.4% (home), but these authors "expect lower agreement for quantity of exposure". Unfortunately, there is no information about whether there were any differential rates among exposed/unexposed or cases/controls. The authors comment that in this study there was no validation of exposure by cotinine, yet the conclusions are largely based on the degree of exposure.

Tunstall-Pedoe et al. [104] provide some direct information on the size of such misclassification in the context of heart disease assessment. Of 807 males and 1520 females who were self-reported smokers, 21 males (2.6%) and 28 females (1.8%) exceeded the serum cotinine cut-off for active smoking. Their comparison between RR estimates based on self-reported exposure in the last 3 days and those based on cotinine results was summarised as follows (p. 142): "Their poor correlation with each other and disparate association with disease undermine the validity of the two measures of passive smoking."

Finally, the very large differences between the results of Steenland et al. [89] and LeVois and Layard [102] are purportedly [89] due in part to misclassification of subjects as indicated by discordance between self-reported and spouse-reported smoking status.

Background exposure

As argued in the United States EPA report [126], one should consider adjusting the RR for general or background exposure to ETS. On the basis of the approach used by Wald et al. [146], applied to the RR adjusted for misclassification and publication bias, we find that an increase of around 0.05–0.10 would occur if one allowed for background exposure. One must, of course, stress the difficulty of doing this adjustment well at these very low levels of estimated RR; the number of assumptions that must be made to carry out any such correction is large. The overall difficulty of getting data to assess such adjustments, and the difficulties of relying on cotinine levels to make the adjustments, are exemplified by Lee [148] and Gross [149], who show that the data used may be seriously deficient and the arguments rely on some unverifiable assumptions.

We conclude that even on the face of it, there is no great support for *strength of association* in this set of studies. Nonetheless, on the basis of the individual estimates and the overall analyses, we do find that chance has essentially been ruled out as a possible explanation of the observed increase in relative risk.

Table 5 Reported dose-response data for mortality from IHD associated with exposure to ETS

First author	Ref.	Exposure measure	Adjustments[a]	Sex	Exposure amount	Reported RR (95% CI)	No. cases	Comments
Hirayama [108]	T1	Spouse cigs/day	a	F	0 ex, 1–19 20+	1.0 1.08 (0.90–1.30) 1.30 (1.06–1.60)	118 240	We verify reported sig. $P < 0.05$ trend
Hole [85]	TVI	Household cigs/day	a	F	0 1–14 15+	1.0 2.09 4.12	3 14 16	Sig. not stated We find NS trend in crude RRs over positive exposures
Humble [87]	p600	Spouse cigs/day	a,b,x					Reported trend only for subgroup HSS whites, $P < 0.06$
Layard [100]	T3	Spouse cigs/day	a,o	M	0	1.0	978	Reported $P = 0.8$.
					<15 15–34 35+	0.76 (0.51–1.14) 1.07 (0.72–1.59) 0.92 (0.33–2.55)	38 45 6	No trend Observed
				F	0 <15 15–34 35+	1.0 0.85 (0.68–1.07) 1.16 (0.94–1.42) 1.07 (0.75–1.53)	459 139 224 52	Reported $P = 0.3$.
Lee [90]	From Lee [103] p. 189	Index: 0 none 1 little 2 average 13–12 lot	none	M	0 2–4 5–12	1.0 0.43 0.43	30 in total	Reported NS trend
				F	0 2–4 5–12	1.0 0.59 0.81	36 in total	Reported NS trend
Sandler/ Helsing [86]	T4	Household cigs/day index	a,z,p,e	F	0 Light: 1–5 Heavy: 6+	1.0 1.20 (1.0–1.4) 1.27 (1.1–1.5)	437 252 299	F: Reported $P < 0.005$ but we find NS for index > 0. M: negligible trend stated
				M	0 Light: 1–5 Heavy: 6+	1.0 1.38 (1.1–1.8) 1.25 (1.0–1.6)	248 56 66	

Table 5 (Contd)

Steenland [89]	T2	Spouse cigs/day	a,r,m,d, w,i,e, l,f,g,ε j,φ	M	< 20	1.33 (1.09–1.61)		No observed trend. Le Vois and Layard [102] also found no trend in this study and CPS-I
					20	1.17 (0.92–1.48)		
					> 20	1.09 (0.77–1.53)		
				F	< 20	1.15 (0.90–1.48)		
					20	1.07 (0.83–1.40)		
					21–39	0.99 (0.67–1.47)		
					40 +	1.04 (0.67–1.61)		
Svendsen [83]	T7	Spouse cigs/day	a,n,γ,e, g,b	M	0	1.0	8	Reported $P = 0.04$
					1–19	0.90	1	
					20 +	3.21	4	
Kawachi [105]	T3	Home or work	see Table 1	F	none	1.0	3	No significance reported
					occasional	1.50 (0.42–5.36)	11	
					regular	2.55 (0.71–9.12)	11	

[a] See Table 2 for definitions

We conclude that there is cause for concern that this significant observed association between IHD and exposure to ETS is influenced by other risk factors (such as diet and previous history) or confounders (such as age and gender) that may have been ignored, difficult to assess and control, or improperly addressed in the design or analysis of the study; we also conclude that demonstrated sources of bias (data dredging, publication bias, misclassification, background exposure) could decrease the observed RRs by an overall amount of around 0.05–0.15 between them.

3.3. Exposure-response data

The existence of an exposure-response relationship is one of the central criteria identified by Hill [7] for the establishment of a causal relationship between an agent and an outcome. This criterion is intended to provide additional support, over and above that of the dichotomous response considered under "strength", for establishing causality.

In Tables 5 and 6 we present details of the exposure-response relationships for heart disease mortality and morbidity, respectively, that have been reported in the various individual studies. There are problems in this area similar to those in the simple assessment of strength of association. Exposure-response relationships are evaluated using arbitrary and inconsistent exposure levels as indicated in Tables 5 and 6. Even using the same measurement as the number of cigarettes per day smoked by the spouse, categorisation varies widely. Moreover, exposure "scores" [90, 109] are seemingly arbitrarily combined. Given the small numbers of cases in these studies, changes in categorisation may result in quite different interpretations of an exposure-response relationship.

That the presence of such a relationship is difficult to evaluate is reflected by the variation in the reviews of the area published to date:

(a) Wu-Williams and Samet [150] report consistently increasing RRs for increasing exposure levels in only two studies [83, 107] but do not report significance levels or confidence intervals for these. They report, in contrast to Wells [15], that the study of Garland et al. [82] shows a decreasing trend for former to current exposure and that two studies [83, 109] show RRs from passive smokers that are at least as high as those from active smokers.

(b) Steenland [9] finds that of the five "best designed and largest" studies, "three showed positive dose-response and two showed positive dose-response for certain subgroups".

(c) Glantz and Parmley [11] state that of the 11 studies of non-fatal cardiac disease (depicted in their Fig. 3), 3 show exposure-response relationships. The particular three are not identified; Wells [15], on whom the authors base their conclusions, reports only two significant trends [82, 86] and, as is seen in Wu-Williams and Samet [150], the former is not an actual trend.

Table 6 Reported dose-response relationships for non-fatal or non-fatal and fatal heart disease associated with exposure to ETS

First author	Ref.	Exposure measure	Adjustments[a]	Sex	Exposure amount	Reported RR (95% CI)	No. cases	Comments
He [94]	T2	Spouse cigs/day	a,o,t,α	F	0	1.0	9	Reported
					1–20	2.30 (0.84–6.33)	12	$P < 0.01$ for all
					21+	6.86 (2.19–21.5)	13	3 analyses
		No years	As above		1–10	1.88		We can only
					11–20	3.07		verify first
					21+	5.49		analysis with
								given data
		Cigarette-years	As above		1–199	1.54		
					200–399	2.30		
					400–599	5.07		
					600+	12.67		
He [99]	p [382]	Spouse cigs/day	a,b,w,β	F				Reported sig. trend in crude RR; NS in adj. RR.
	TVI	Work place ETS	As above and δ	F	0	1.0	26	$P = 0.022$
					6–10	0.87 (0.3–2.53)	10	
					11–20	2.95 (1.05–8.28)	15	
					20+	3.56 (0.81–15.6)	8	
		Duration (years)	As above	F	6–15	3.08 (0.9–10.58)	8	$P = 0.12$
					16+	1.56 (0.67–3.64)	25	
		No. of smokers	As above	F	1–2	1.16 (0.48–2.82)	36	$P = 0.024$
					3	5.06 (1.42–18.0)	6	
					4+	4.11 (0.39–43.7)	1	
He [99]		Exposure time daily (h)	As above	F	1–2	0.62 (0.22–1.80)	30	$P = 0.002$
					3–4	4.03 (1.33–12.3)	30	
					5+	21.3 (2.71–168)	2	
		Cumulative exposure	As above	F	1–2000	1.00 (0.39–2.57)	13	$P = 0.003$
					2001–4000	2.05 (0.47–8.87)	5	
					4000+	9.23 (2.01–42.3)	15	
	TVII	Spouse & work Cumulative exposure Cig/day*yr	a,u	F	1–499	1.79 (0.65–4.92)		$P = 0.022$
					500–999	2.55 (0.92–7.10)		
					1000+	3.95 (1.03–15.3)		
		Cumulative Exposure as a score	As above	F	Low	1.75 (0.68–4.46)		$P = 0.008$
					Medium	3.11 (1.06–9.12)		
					High	7.61 (1.15–50.2)		
Hole [85]	TVI	Household cigs/day	a	F	0	1.0	17	No comment on
					Low: 1–14	1.14	32	trend by authors
					High: 15+	1.61	31	
La Vecchia [98]	p [505]	Household cigs/day	k,a,e,h, b,i,f,d	F,M	0	1.0	17	Reported
					Ex-	0.91 (0.36–2.28)	11	general NS
					< 15	1.13 (0.45–2.82)	13	We find NS
					15+	1.30 (0.50–3.40)		trend
Martin [91]	Abst-ract		1: none 2: c,m,d,n, g,j	F	1: ex- 1: current 2: current	1.9 4.4 3.4	23 in total	Significant observed trend
Muscat [101]	T2	Childhood exposure duration (years)	a,b,e	M	1–17	0.9 (0.4–2.1)	68 in total	Reported no trend
					>17	0.7 (0.3–1.6)		
				F	1–17	0.6 (0.2–2.0)	46 in total	
					>17	0.8 (0.3–2.2)		
	T2	Adult exposure duration (years)	As above	M	1–20	1.7 (0.7–4.5)	As above	Reported no apparent trend
					21–30	1.5 (0.4–5.2)		
					>30	1.1 (0.4–2.8)		
				F	1–20	2.0 (0.5–8.1)		
					21–30	0.9 (.2–4.4)		
					>30	1.7 (0.5–5.9)		
	p. 717	Adult pack-years	As above	M	1–10	1.2	As above	Reported similar pattern
					>10	1.3		
				F	1–10	2.3		
					>10	1.6		

Table 6 (Contd.)

Palmer [92]		Spouse	"Known risk factors"	F				Observed trend
Svendsen [83]	T7	Spouse cigs/day	a,b,e,g,n	M	0 1–19 20+	1.0 1.20 1.75	48 8 13	NS trend
Tunstall-Pedoe [104]	T3[b]	Reported exposed in last 3 days	a,z,v,b	F,M	None Little Some A lot	1.0 0.8 (0.4–1.7) 1.6 (0.8–3.1) 2.4 (1.1–4.8)	16 16 21 17	Significantly raised in high-exposure group
		Serum cotinine	a,z,v,b	F,M	Group I Group II Group III Group IV	1.0 1.5 (0.8–3.0) 1.7 (0.8–4.4) 2.7 (1.3–5.6)	15 20 19 16	Stronger gradient than for self-report
Kawachi [105]	T4	Duration of adult life living with smoker (yrs)	See T1	F	<1 1–9 10–19 20–29 ≥ 30	1.0 1.19 (0.75–1.90) 1.54 (0.99–2.40) 1.11 (0.69–1.77) 1.50 (0.97–2.32)	159280 61759 55409 48376 31	No. cases in person-years Significance not stated
Ciruzzi [103]	Abs	Spouse cigs/day	a,k,e,i, s,d,m,c	F,M	1–20 >20	1.27 (0.7–2) 2.41 (0.8–7)		Significance not stated

[a] See Table 8 for definition
[b] Reported results for Tunstall-Pedoe et al. [104] are for diagnosed CHD. Reported dose-response relationships are not seen for all outcomes

(d) Gori [12] mentions exposure-response in relation to only two studies [100, 109] and reports no apparent exposure-effect gradient in either.
(e) Law et al. [13] assert a significant overall dose-response relationship, based on a formal meta-analysis model taking age into account, but the data supporting this assertion are not provided and the methodology is not sufficiently well enough described to enable reproduction of the results.

In an effort to reconcile this confused picture, we provide below a review of the exposure-response relationships between ETS and IHD. Consideration of the studies in Tables 5 and 6 reveal the following:

1. Of nine studies that report exposure-response relationships for mortality:
   (a) Only two studies [83, 108] claim statistically significant trends for all subgroups. Of these, the former has very small numbers of exposed cases and, moreover, is based on a high-risk population sufficiently non-representative that it is omitted from a meta-analysis by Wells [15].
   (b) Helsing et al. [109] report a significant trend for females but a negligible trend for males.
   (c) Six studies find no significant relationship: Humble et al. [87] report a significant trend for only one subgroup; Hole et al. [85] find a (nonsignificant) consistent increase in RR with increasing exposure; Steenland et al. [89] find such consistency only for females, and Layard [100] and Lee [90] also do not show a positive trend over positive exposure categories. It should be noted that LeVois and Layard [102] also find no positive trend for either the CPS-I or the CPS-II study. A consistently increasing trend is observed in [105] but is based on small numbers and significance is not stated.
2. Of eleven studies that report dose-response relationships for non-fatal heart disease:
   (a) Two studies [91, 94] report a statistically significant trend for exposure to spousal smoking. However, for the first study the trend is only over ex- and current smokers and is not verifiable with the given data, and for the second study this observation is not apparent in a similar population [99]. One further study [103] finds an increased RR with increased spousal smoking but the corresponding confidence intervals are extremely wide and encompass unity.
   (b) One study [99] reports generally significant trends for exposure at work and for combined exposure at work and home.
   (c) Two studies [85, 98] report an observed trend, but in the former study there is no comment on the significance of the trend and in the latter a general lack of significance is stated.
   (d) Two studies [101, 102] find no trend.
   (e) One study [104] reports a consistent increase in response for questionnaire angina and all CHD based on self-reports and no such increase based on serum cotinine. No dose-response is found for undiagnosed CHD. A relationship is found for diagnosed CHD but the significance is not stated. The authors identify significant RRs at the highest exposure levels, but this may be a result of confounding between overall raised RR.
3. Of three studies for which the outcome is either mortality or morbidity, only one reports a statistically significant trend. Palmer et al. [92] simply state

that a trend was "observed" and Svendsen et al. [83] observe a nonsignificant but consistent increase in RR with increasing exposure categories. Kawachi [105] only report significance ($P=0.002$) for the trend in our Table 3. A consistent trend was not found for duration of living with a smoker, despite large numbers. This analysis, apparently based on 38,025 women (176 cases), which is almost 6,000 more than the 32,046 reported to be in the study, reports trend figures that are inconsistent with the analyses of overall RR.

There are only three studies (Hirayama [88], females in Helsing et al. [109] and one of the He et al. [99] subgroups) for which we can verify a significant trend. He et al. [99] caution, however, that the trend found in their study "is not precise enough for risk assessment for unit dose of exposure". Indeed, the influence of small sample sizes in some of the exposure categories must not be overlooked. On the one hand, the results of Svendsen et al. [83], for example, are based on only 1 death in the 1–19 cigarettes exposure group. On the other hand, this lack of power may serve to muddy any true relationship.

This raises two important issues. First, is it possible to test for an overall trend based on the data? Second, even if such an hypothesis of homogeneity of RR across exposure categories can be tested and is found to be supported, can we develop a model to describe the exposure-response relationship? The latter may be very difficult, especially with respect to threshold effects (for small or large exposures) or deviations from a linear relationship, with the typically small amount of data and the inconsistent definitions available from these studies. The biological evidence fuels this debate. For example, the NHMRC report [6] (p. 155) proposes that evidence of a saturation effect admits a possibility of a threshold effect at some high exposure.

It is apparent in Tables 5 and 6 that there is such variation in RR at each exposure level that any quantitative estimate of a biological gradient is impossible. This is graphically depicted in Figs. 6 and 7, which indicate the size of the 95% confidence intervals for RRs reported using exposure in terms of cigarettes/day. These are plotted around the midpoint of each exposure category; open-ended categories are allocated the same increase in exposure as the previous category. The general "muddiness" of these pictures, resulting from inconsistency both

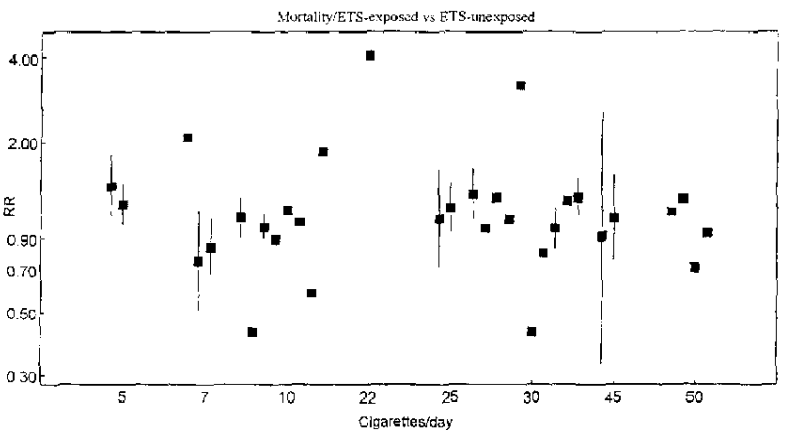

Fig. 6 Relative risks (on a logarithmic scale) for mortality at various levels of exposure from all available studies. Where available, 95% CIs are shown; otherwise, only point estimates are given

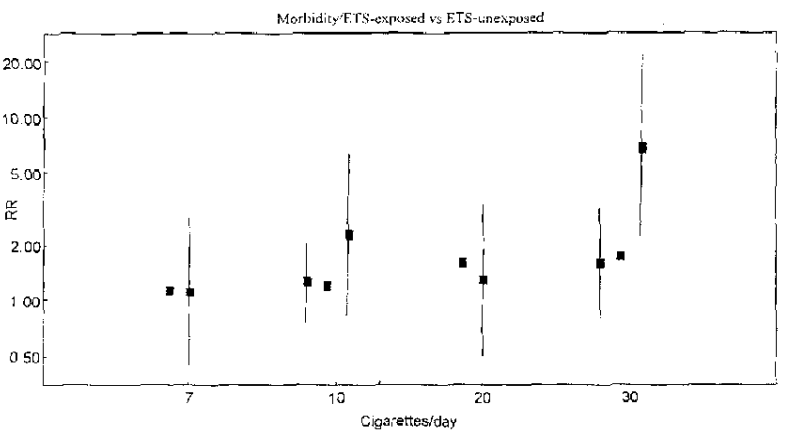

Fig. 7 Relative risks (on a logarithmic scale) for morbidity at various levels of exposure from all available studies. Where available, 95% CIs are shown; otherwise, only point estimates are given

Table 7 RRs of IHD associated with exposure to former and current smokers

First author	Ref.	Outcome	Exposure source	Sex	Exposure measure	Reported RR (95% CI)	No. cases
Martin [91]	Abstract	Morbidity	Spouse	F	Ex-	1.9	
					Current	3.4	
La Vecchia [98]	p. 505	Morbidity	Household	F	Ex-	0.91 (0.36–2.28)	17
					< 15	1.13 (0.45–2.82)	11
					15+	1.30 (0.50–3.40)	13
Butler [84]		Mortality	Spouse	F	Ex-	0.96 (0.6–1.7)	
					Current	1.40 (0.51–3.84)	
Garland [82]	Table 2	Mortality	Spouse	F	0	1.0	2
					Ex-	3.0 (=3.6/1.2)	15
					Current	2.25 (=2.7/1.2)	2
Steenland [89]	Table 2	Mortality	Spouse	M	Ex-	0.96 (0.83–1.11)	
					Current	1.22 (1.07–1.40)	
				F	Ex-	1.00 (0.88–1.13)	
					Current	1.10 (0.96–1.27)	

within and between studies, seem to prohibit a general meta-analysis of exposure-response as in Tweedie and Mengersen [14]. Moreover, any extrapolation to low or high exposures must be viewed with extreme caution, especially if the biological evidence is mixed [72].

Former versus current exposure levels

Despite the lack of dose-response seen in most studies, a weaker biological gradient might be asserted if there were an established difference in RR between subjects formerly and currently exposed to ETS. Some reviews accept a biological premise behind such a gradient, namely, that the risk of heart disease is increased with current exposure to ETS and declines quickly when exposure ends. This may apply if ETS acts to enhance thrombogenesis in persons with preexisting IHD. (See, for example, the reply by Steenland et al. [117].)

This premise implies, if it holds in a strong sense, that RRs for those married to former smokers should be close to unity. Even if the decline is not this strong, those married to active smokers should at least have higher RRs than spouses of former smokers. Table 6 provides RRs reported for subjects exposed to former and current smokers. Three studies support the strong form of the biological argument [84, 89, 98], but in two of these studies the RRs recorded for subjects married to current smokers are noticeably lower than most; thus, this could be an artefact of the control group. In the other two studies [82, 91], subjects exposed to former smokers have RRs at least as large as those noted for subjects exposed to current smokers in the other studies; moreover, the RR recorded for subjects exposed to current smokers as compared with former smokers varies (from 1.8 [91] to 0.76 [82]), which does not seem biologically rational. On the basis of these observations, we conclude that overall there is no established trend in RR over former and current exposure categories and there is little support for a biological gradient on these grounds.

This range of data must also cast some doubt on those studies that combine former smokers with other groups. For example, Hirayama [88, 107, 108], LeVois and Layard [102] and Layard [100] apparently combine subjects married to former smokers with current smokers, which might be supportable on the basis of the data of Martin et al. [91] and Garland et al. [82], but not of those of La Vecchia et al. [98] or Butler [84] or of the biological model supported by some reviews [6, 13].

This model would indicate that it may indeed be more appropriate to include the ex-smokers in the reference group or to exclude them entirely. Such differences in combination can have considerable impact on the results; for example, in Garland et al. [82], if subjects married to former and never-smokers are combined as a reference group, the RR for women married to current smokers drops from 2.25 to 0.76. We have no way of knowing how different combinations of reference groups might have changed the conclusions of Hirayama [88, 107, 108], but we do know that it makes a substantial impact in the analysis of the CPS-II cohort data [89, 102].

We conclude that the support for an exposure-response relationship in the studies of exposure to ETS and incidence of IHD has been overstated in the literature and that there are indeed few data indicating that such a dose-response relationship exists.

3.4. Consistency

The criterion of consistency of association is an obvious requirement, but its interpretation can be rather subjective due to (a) different approaches to the identification of suitable estimates from individual studies, as discussed above, and (b) the criteria used to judge the consistency of these estimates across studies.

All studies in Table 1 provide some information on the RR of IHD (variously defined) associated with exposure to ETS as measured by spousal smoking, but the

corresponding RRs in Table 3 are quite variable. The majority, but not all, are positive; the point estimates vary from 0.93 to 9.95. Moreover, results of new studies have not "settled down" to give more consistent values, as one might expect with more refined analyses of an emerging causal relationship, and there is no strong consistency between estimates from different sources of exposure, as can be seen in Table 4.

It can, of course, be seen in Table 1 that the studies have been conducted over different periods and with quite different populations. Although this may lead to questions of representativeness and, hence, to difficulties with extrapolation of the reported results, it does indicate that the association has been tested under different circumstances. However, for consistency of an association the observed effect also needs to be similar, and this is clearly not the case.

An obvious question is whether the lack of consistency is simply due to one or more confounders across studies. An example of this is the age of subjects; Sandler et al. [86] set a minimum age of 25 years, Garland et al. [82] consider only subjects aged 50–79 years, and Kawachi et al. [105] consider only nurses who are aged around 25–55 years at the beginning of their 10-year study. We find, however, no interpretable pattern in RR across the different age groups.

We conclude that that there is a considerable lack of consistency in reported results between individual studies. Moreover, from earlier discussion we conclude that there is also inconsistency in the identification and reporting of relevant results from these studies.

3.5. Specificity

To assess more completely specificity and its role in the causality criteria, following Hill [7] we propose a threefold expansion of this criterion: specificity of magnitude, specificity of exposure, and specificity of response.

Specificity of magnitude

Hill [7] notes that assessment of specificity of magnitude may be defined in the light of test 3 and after comparison with RRs of other outcomes. For example, if other causes of death are raised 50% in those exposed to ETS, whereas IHD, say, is raised 1000%, then there is specificity of magnitude. From the above discussions the epidemiological studies fail such an assessment. It becomes more important, then, to consider the next two aspects of specificity.

Specificity of exposure to ETS

This is unanimously acknowledged as difficult to assess since the exposure itself is difficult to define and measure. Below, we consider the various definitions that are employed in the IHD studies.

From a biological perspective, exposure to ETS is in effect an indirect measure of intake of various particulates. In a summary of the available ETS exposure data, Guerin et al. [151] indicate that virtually all ETS constituents have multiple sources, and they claim that for the most part the ETS contribution to such constituents above normal background levels may be small and difficult to quantify. (See also Friedman et al. [152])

Most epidemiological studies consider exposure in terms of spousal smoking, with the most common categorisation being never-smoker, ex-smoker and current smoker and the quantification of current smoking being done in terms of the number of cigarettes per day smoked by the spouse. Even within this definition there are differences. Lee et al. [90] measure spousal smoking of manufactured cigarettes during the whole of the marriage. Sandler et al. [86], Hole et al. [85], Dobson et al. [95] and Kawachi et al. [105] define exposure in terms of cohabitants (not necessarily the spouse), and their definitions differ with respect to the time of exposure. He et al. [99] define passive smoking from the spouse as "living with a smoking husband for over 5 years" and report five different measures of exposure at work (Table VI).

Poor control over exposure measurement may result in inconsistent results within a study and may indeed mask other potential biases. As an illustration, Kawachi et al. [105] base analyses on a simple baseline question, "Are you currently exposed to cigarette smoke from other people?" at home and in the workplace, and categorise subjects into three levels of exposure (none, occasional, regular). There is no information about whether exposure was maintained over 1982–1992. This is a real problem if the risk of CHD decreases quickly after cessation of active or passive smoking. Since, as the authors acknowledge, there has been a very strong move away from smoking in hospitals (and also in the home, to a less well documented extent) over the study period, there must be a very high likelihood that the "exposed" group was not exposed over a very substantial part of its person-years. (There is also, of course, a possibility that the control group became contaminated by later exposure, although there is less reason to think that this might have happened.) The question of whether this results in a conservative estimate is, however, debatable. The standard argument is that if the RR is raised, then there is an excess of incidence in the exposed group as compared with the control group, but if there are controls in the supposedly exposed group, they have the same risk as the real controls, the result being that all the excesses are due to the (smaller) real exposed group and the rate of excess in the real exposed group is even higher than that observed. The implicit assumption that the misclassified group is the same as the controls may be crucial in this sense. If the control group indeed had a low incidence rate, as may be the case in this study, the effect may be reversed and the RR may actually be overstated. Kawachi et al. [105] did attempt further as-

sessment of misclassification through classification of cases into two categories of diagnoses: "definite" and "probable". Definite diagnoses comprised 84% of those included in the analysis; in the text (p. 2376) a comment is made that those in the "definite" group showed marginally higher relative risks overall than did both the "definite" and "probable" groups combined.

Knowledge of cohabitation with a smoker does not necessarily imply exposure, nor is the "unexposed" group necessarily unexposed [137]. The impact that this variation will have on the RR depends crucially on the shape of the true exposure-response relationship. Misclassification bias makes lack of specificity of exposure particularly troubling. As mentioned above, there may be serious and systematic flaws in the allocation of individuals as unexposed to active smoking but exposed to ETS. Time of exposure, degree and duration are all important issues in defining exposure, but problems of recall and the comparative rarity of the disease make more precise categorisation difficult to achieve accurately. Indirect reporting of subject and spousal status can pose problems in principle as well and is a subject of current debate about the analyses of the CPS-I, CPS-II and NMFS studies [111–113]. In Svendsen et al. [83] the spouse's smoking status was based on the husband's report. It is not clear in Hirayama [88, 107, 108] whether the subjects or the spouses provided information about spousal smoking habits.

Lee et al. [90] provide empirical evidence of misclassification of spousal smoking status using interviews of the spouse, the index patient, and both sources of information. RRs varied considerably, for example, from 0.75 (based on index patient information) to 1.60 (based on spouse information) for females, but no consistent pattern was observed. Discrepancies were seen for 15% of spouses with respect to smoking at some time during the marriage and for 3% with respect to smoking during the year of hospital interview. Quite different RR estimates resulting from moving of a small number of cases between categories of exposure are revealed in the study of Tunstall-Pedoe et al. [104] in their comparison of estimates based on serum cotinine and self-reporting for subjects exposed over the last 3 days.

Specificity of response

The definition of heart disease induces some lack of specificity of response. Although all studies measure IHD as an outcome, three particular outcomes are actually identified: death, non-fatal IHD event, or both fatal and non-fatal disease. Further refinements are undertaken in individual papers. For example, Tunstall-Pedoe et al. [104] consider five categories of non-fatal CHD. We do not know whether the risks associated with these events are equivalent; if they are not, the problems of non-specificity of response are clear, and comparison and combination of results within and between different studies should be done with caution.

Misclassification of outcome could also cause problems. Death certificates, used in two studies [86, 88], are an acknowledged source of potential misclassification. Some published estimates of misclassification due to reliance on death certificate information for lung cancer range from 8% [153] and 10% [154] to over 25% [155–157]. Lee et al. [90] use hospital records in the ascertainment of cases; in his study of ETS and lung cancer, Garfinkel [3] found a strong association based on hospital records but detected a much weaker association after partially correcting for the bias that this induced.

One of the strengths of the study by Kawachi et al. [105] lies in what appears to be good control over measuring the outcome, including the fact that physicians were blinded when assessing non-fatal MI, that there was corroboration of death certificate information, and that there was almost complete capture of all fatal MI in the cohort. Even in this case, however, the outcome measure has some peculiar features. The exclusion of subjects with incidence of CHD at each 2-year round of the study makes it difficult to define the endpoint and to interpret and compare the resultant RR estimates. Moreover, there is some ambiguity over how a subject with a non-fatal and then a fatal incident was counted; this does not affect the overall RR but might affect the rates recorded for morbidity and mortality separately.

He et al. [99] report that 26 of 84 patients originally diagnosed with cardiovascular disease were subsequently confirmed by coronary arteriography to be normal. This group was reportedly not different from other controls with respect to the proportion exposed, but they were indeed different from cases. Hence, if they had been included as cases the true RR would have been overestimated.

Several other biases are also possible. There is clearly a difficulty in asserting causality if the studies are of poor quality in design, conduct and analysis; thus, biases might of themselves give rise to the observed association. It is not clear where an assessment of quality should go in the Hill [7] criteria, which rather optimistically perhaps do not allow that such flaws might exist.

As an example, control of non-response and loss to follow-up differ dramatically between studies. At least four papers report high non-response rates (20% [85], 18% [82], 20% [94], 20–37% [95]), and subjects lost to follow-up vary dramatically from none [83] to 85% [86]. Criqui et al. are reported by Dobson et al. [95] to have examined differences between respondents and non-respondents in a population-based cardiovascular disease study; their conclusion is that "people who respond to risk factor surveys are less likely than non-respondents to be smokers". This is supported by Dobson et al. [95], who compare non-respondents and respondents with respect to smoking prevalence rates and conclude that non-response among control subjects can lead to underestimation of the prevalence of smoking and, consequently, to an overestimation of RR. Given that smokers tend to be married to smokers [110], such a bias would also apply to studies of ETS based on spousal exposure.

The role of specificity in causality

It is not atypical for epidemiological agents to fail the test of specificity, more or less without prejudice. This is the case for this particular relationship, as demonstrated above and acknowledged in various reviews; see, for example, Table 6.5 in the NH&MRC report [6], which states that "This criterion has not been met for the relationship of either active or passive smoking to ischaemic heart disease".

This does not necessarily lead to rejection of the hypothesis of causality. It does, however, point to the need to consider the role of all of the alternative explanations in assessing the relationship in question. For non-specific causes, one needs to ensure that the various other known causes or potential causes of the disease have been excluded as confounding factors before any strong claims are made.

We conclude that specificity of magnitude, exposure and response are all unsupported, and although in epidemiological studies this is not a major negative, it does not add weight to a causal argument.

4. Mixed biological and epidemiological criteria

4.1. Overall conclusions

Temporality is a criterion whose failure is of importance but whose verification is not. In this context it is relevant to consider it in both the experimental and the epidemiological contexts. When the criteria of analogy and coherence are considered there is a clear contradiction that needs explanation. Our view is that this is not so much a failure of the coherence criterion as a failure of the analogy criterion as detailed earlier. If we accept that MS and ETS do not function similarly for any of the reasons given in the literature, then we cannot claim that causality is supported by any analogy with active smoking, but nor do we have to go into tortuous explanations in trying to cover the lack of coherence between results for the two. The lack of an argument by analogy does not negate any other causal argument, but it does mean that conclusions about active smoking are not strongly relevant to conclusions about ETS and do not bolster the argument for causality.

On the basis of the analysis below, we find the following:

Test 7 (*temporality*): we conclude that in general populations, causality cannot be ruled out on this criterion and that for those with pre-existing heart conditions it is clearly satisfied.

Test 8 (*argument by analogy*): there is no strong basis at this stage to argue that ETS causes IHD on the basis of analogies with the actions of MS. Whereas some authors dispute the analogy on the basis of constituent differences, virtually all seem to agree that the observed associations are possible only if the mechanisms are different.

Test 9 (*coherence*): if one assumes that ETS is indeed different in its action from MS, then the major lack of coherence in the epidemiological studies is removed. If one does not accept this, then there is a serious lack of coherence in the literature.

4.2. Temporality

Did the exposure precede the outcome? It is important that the definitions used in the study and the questions asked of subjects address this point. It is potentially invalid to establish an association based on current exposure if exposure has changed over time. In the studies of IHD the outcome of analysis may depend on when the exposure is measured. Hence, measures of current exposure may be irrelevant without assumptions of constancy of exposure and confounders over time, whereas past exposure requires recall with associated possible bias. Thus, temporality is harder to establish than might be expected, although Wexler [155] (p. 150) asserts that each of the epidemiological studies carried out up to 1989 appears to provide an adequate temporal association between ETS exposure and the onset of cardiovascular disease.

However, for one sub-group of the general population, namely, those with pre-existing IHD, past exposure may be of less importance than recent exposure since it is argued (see above) that ETS may affect risk by enhancing acute episodes of thrombogenesis through one or more of a number of different pathways.

We conclude that it is (perhaps surprisingly) difficult to find conclusive evidence that the temporality criterion has been satisfied, but there is no indication that it has been failed.

4.3. Analogy and coherence

Relations between analogy and coherence

These two criteria are rather different. Reasoning by analogy, if passed, provides a potentially positive criterion; coherence, if failed, provides a potentially negative criterion. If the proposed relationship is analogous with some other accepted cause and effect, we might weaken the requirement for direct biological plausibility of the proposed relationship. In the case of ETS, analogies with outcomes from mainstream smoking (MS) are made on the basis that, e.g., the chemical composition, exposure levels and inhalation patterns from the two types of smoke are claimed to be similar in relevant respects.

This is, of course, a tempting analogy and, on the face of it, an easy one to make. Many authors [9, 11] draw

attention to the role ascribed to MS as a risk factor for IHD by the United States Surgeon General [1] and leave the impression that this clearly supports the argument by analogy. Wells [15] quotes the United States Surgeon General in asserting that "active smoking is a well known cause of IHD"; he claims that ETS contains the chemicals "thought to be most important in causing IHD ... although they are diluted considerably by the ambient air" and then concludes that "logically one would expect ETS exposure to result in IHD at a lower level than that from active smoking".

We must believe that, precisely because of this last argument, in this context one must deal with the analogy test in conjunction with the test of coherence, which asks whether causal inference from the observed data on the relationship are coherent with those known findings about related issues. It seems to be unarguable that if the relationship of IHD incidence with ETS is analogous to that of MS, then related results should be coherent. However, the lack of coherence (or analogy) in this case is quite marked. One would expect, based on the data obtained in lung cancer studies and the known low "dose" of ETS as compared with MS, that the RR of ETS should be smaller by a very considerable amount than that of MS. Yet many authors have noted the lack of coherence between the results observed in epidemiological studies of the RR for IHD and exposure to ETS (which average around 1.2–1.4 and range up to almost 3) and the RR for IHD and MS itself (which are usually cited from the United States Surgeon General [1] at around 1.7 on average).

This inconsistency is discussed in some detail in the NH&MRC report [6], where differences in the chemical composition of ETS and MS smoke, the saturation effect on platelet aggregation, the underestimation of IHD associated with active smoking, and possible bias and confounding are proposed as possible explanations. This is even more striking if one considers only low-dose studies of MS, where the RRs seem to be, if anything, smaller than those of ETS. Hence, there is a real issue of coherence to be addressed if one accepts the argument by analogy, and we consider this in detail below.

Several arguments have been put forward to help explain this lack of coherence, and these will now be considered in more detail, addressing in order (a) the different constituents of MS and ETS, where we conclude that the analogy argument still seems plausible; (b) a lack of coherence between low-dose MS and ETS results; and (c) possible explanations of the "paradox" in the literature, such as reference group changes, toxicity questions, and the difference in reaction of active and passive smokers. After considering these issues we will conclude that the analogy argument is not valid. Indeed, we show below that in the scientific literature the analogy argument has been strongly discounted by virtually all authors, at least implicitly, even if the lack of analogy is not drawn by them as an explicit conclusion of their other observations.

Constituents of MS and ETS

Any analogy with active smoking requires consideration of equivalence between MS and ETS constituents, consideration of exposure levels thought to be analogous with ETS exposure, and assessment of the effect of the level of active smoking at these levels.

Steenland [9] argues that the constituents of MS and ETS are sufficiently different that "arguments inferring ETS health effects based on known health effects of MS are not appropriate". Gori [12] also says, in arguing that ETS is not harmful as compared with MS, that "... their chemical and physical differences are substantial... [and]... chemical and biological activity of ETS is less than that for MS". Steenland, unlike Gori, is claiming that the differences are such that ETS is possibly more likely than MS to be harmful. However, whatever the differences, if they are accepted, this would immediately stop the analogy argument.

Conversely, there seem to be enough data to convince other authors [11, 15] that various constituents of MS (e.g. CO, nicotine, polyaromatic hydrocarbons) are present in ETS that might be associated with initiation or aggravation of IHD. At this step, then, there is debate over the validity of the analogy and, hence, it still seems appropriate to pursue the analogy argument. Note, however, that the existence of these constituents is used in meeting the criterion of test 1, namely, that of direct biological plausibility. The argument that ETS has analogous constituents to MS therefore adds nothing extra (over test 1) to the consideration of causality.

Lack of consistency between low-dose MS and ETS

What would be required for the argument by analogy to be credible would be to establish the effect of an exposure to the constituents of MS at levels comparable with those of ETS exposure and then to indicate that the effect is repeated for ETS.

The appropriate exposure level, if any, is a debatable issue. Cotinine studies have been used to determine that non-smokers exposed to spousal smoking have perhaps the equivalent of one cigarette per day or less [11, 15, 158]. Arguing in the opposite direction, from evaluations of indoor air constituents, Gori [12] asserts that the level of exposure of the passive smoker is one cigarette per year. Whatever the exact number, there appears to be no disagreement that ETS exposure from all sources in, say, Australia or the United States is equivalent to no more than two to three cigarettes a day at the very most and is probably very considerably less, even in the "high-dose" range. It is thus this range of active smoking that we need to consider.

Let us assume that the analogy argument is valid. Then, clearly, ETS should be associated with the same amount of IHD as some low dose of MS. If it is not,

Table 8 Low-dose RRs for active smoking and IHD

Study	Sex	Age (years)	Cigs/day	RR
Hammond and Horn (1958)[a]		Unknown	1–9	1.3
Lossing, Best (1966)[a]		Unknown	1–9	1.6
Cederlof (1975)[a]		Unknown	1–7	1.5
Doll and Peto (1976)[a]		Unknown	1–14	1.5
Rogot and Murray (1980)[a]		Unknown	1–9	1.2
Doll and Peto (1976)[b]	M		1–14	1.2
Doll and Peto (1976)[b]	F		1–14	0.96
Doll and Peto (1980)[b]	M	65+	1–14	1.38
Doll and Peto (1980)[b]	F	65+	1–14	0.79
Doll and Peto (1980)[b]	M	45–65	1–14	1.58
Doll and Peto (1980)[b]	F	45–65	1–14	1.42
US Veterans (1980)[b]		Unknown	1–9	1.2
Framingham (1984)[b]	M	35–64	1–10	1.08
Framingham (1984)[b]	M	65–94	1–10	0.95
Framingham (1984)[b]	F	35–64	1–10	1.00
Framingham (1984)[b]	F	65–94	1–10	0.96
Bush and Comstock[b]		25–44	1–9	0.89
Bush and Comstock[b]		45–64	1–9	1.25
Dagenais (1990)[c]	M	35–64	1–20	1.4
Gramenzi (1989)[c]	F	24–69	1–14	2.28
Higenbotham (1990)[c]	M	40–64	1–9	1.44
Mant (1987)[c]	F	25–39	1–14	2.64
Palmer (1989)[c]	F	25–64	1–4	2.4
Rosengrun (1990)[c]	M	47–55	1–4	4.6
Shaten (1991)[c]	M	35–57	1–15	1.37
Tverdal (1993)[c]	M	35–49	1–9	3.25
Tverdal (1993)[c]	F	35–49	1–20	1.81
Willett (1987)[c]	F	30–55	1–4	2.4

[a] Referred to in Wu-Williams and Samet [150]
[b] Referred to in Gori [12]
[c] Referred to in English et al. [159]

then there may be other different reasons (such as different constituents) that still imply that ETS causes IHD, but the argument by analogy no longer provides support for the inference of causality.

In Table 8 we tabulate the low-dose RRs observed across a range of studies of MS. This is meant to be not exhaustive but rather illustrative. It is, however, striking that there is no commonality between the studies in the three sources cited [12, 150, 159] [except for Doll and Peto (1976), which seems to be misquoted in Wu-Williams and Samet [150]].

The simple average RR of these low-dose results is 1.65, although this is raised by the inclusion of the studies of lower age groups by Mant, Rosengrun,Tverdal and Willett; in the first two referenced sources [12, 150] the average is 1.2, and the highest observed RR in those is 1.6. The low exposure from the Framingham study indicates no excess risk at all in any age group at this exposure level. Many writers have noted that this is in considerable contrast to the range of observed RRs associated with ETS, with the median being 1.3 and some values well in excess of 2.0. This is especially of concern when one notes that the exposure range in Table 8 is usually at least 2 or 3 times the range corresponding to ETS "dosage", any extrapolation to a 1–3 cigarettes/day exposure range would be, on the face of it, consistent with an RR of only 1.1–1.2, or perhaps rather less. This is in direct contrast to the results of Law et al. [13], who provide an extrapolation to one cigarette per day as based on five cohort studies and predict an RR of 1.39, thus claiming coherence with the ETS estimate of 1.3.

Possible explanations and their relation to the argument by analogy

There are several things that might cause a somewhat "non-coherent" result. We now review the comments of a number of authors concerning possible explanations of the differences between the results that the "coherence" approach should give and the observed results, and we note that if any of them are correct, they preclude the analogy argument from consideration.

First, there is an argument [6, 9] that the RRs for ETS and MS are based on dissimilar reference groups. For MS the group includes those exposed to spousal smoking; thus, the RR is deflated as compared with that recorded for those exposed to ETS, for whom the reference group is those exposed only to background ETS at the most. This has some validity. However, one can adjust the RRs in Table 7 to account for this reference change and find that the excess risk for MS rises by perhaps 20% when put on this comparable basis. This does not seem enough to change the inconsistency of the results.

Second, there is the argument that the constituents of ETS may be more toxic than those of MS; even if the exposure is low as measured (say) by cotinine, some

other toxins may be higher in ETS than in MS. This is a rather hard argument to justify. Wu-Williams and Samet [150] conclude that "it is difficult to reconcile the relatively similar risk patterns for IHD among active smokers and nonsmokers exposed to ETS since active smokers receive at least the same passive smoke as nonsmokers in addition to the exposure of active smoking." In other words, it is not easy to believe that even if ETS is more toxic, the amount received by the spouse of an active smoker is greater than the amount received by the actual active smoker.

Steenland [9] goes further and argues that ETS may actually be different; the reason for the relatively high RR noted for ETS may be that "sidestream smoke is qualitatively different from mainstream smoke, and exposure to sidestream smoke may be proportionally more toxic to the heart than mainstream smoke." The NH&MRC report [6], in discussing reasons for this lack of comparability, states that "the chemical compositions of ETS and of the smoke inhaled by active smokers are different" and that there could be qualitative differences in the pathways relevant to active and passive smoking. It is hard to maintain, if we accept these statements, that the argument by analogy is strongly supported, since it implies that we do not have analogous substances.

Third, there is the argument that non-smokers exposed to ETS react differently than do active smokers to MS or ETS. This overcomes the problem that active smokers are also exposed to ETS. Glantz and Parmley [11] follow this line. They say that "the qualitative differences between the effects of ETS on smokers and nonsmokers explain the high RRs associated with passive smoking compared with active smoking" because, they claim, in smokers "the cardiovascular system ... adapts to compensate for the deleterious effects of smoking" and "smokers may have achieved the maximum response possible to at least some of the toxins in the smoke, so the small additional exposures associated with passive smoking have little or no effect."

Leaving aside the odd observation that at low exposure levels of MS this "maximum response" seems to lead to RRs lower in general than those obtained from the "small additional exposures" to ETS (even though active smokers must be exposed to ETS on top of MS), this argument seems to imply without doubt a conclusion that ETS in non-smokers is different from MS in active smokers and, hence, that one cannot consider the effect of ETS on the basis of an analogy with MS.

Other areas of coherence

We must also take into account the links between the epidemiological studies and other related sources of data. In particular, it has been noted [12] that in some countries, extra cigarette consumption has been associated with decreasing incidence of IHD. There seem to be difficulties with relating this to the overall causal argument, since the very multi-factorial nature of IHD could mean that the incidence of the disease is dropping because of much more complex changes in the other factors related to IHD. We do not pursue this further herein as a consequence.

There might be some grounds to argue that ETS causes IHD on the basis of the analogies with the actions of MS, whereas the lack of coherence with the MS data goes somewhat against an argument for causality. This seems best resolved if one assumes that ETS is indeed different in its action from MS, as then the major lack of coherence in the epidemiological studies is removed, although one can no longer use analogy with MS to build a causal argument.

A recent ruling of the United States Court addressed precisely this issue of analogy in considering a United States Environmental Protection Agency (EPA) evaluation of the relationship between lung cancer and ETS. The court ruled, amongst other things, that the EPA had been incorrect in using the analogy argument, and that in fact the EPA report had asserted the analogy did not exist in other parts of its discussion. The conclusions of the court are rather similar to those above. They find that one cannot use the analogy and then claim coherence, or vice versa.

5. Discussion

5.1. The value of the causal criteria

One of the clear results of our evaluation is an appreciation of the cumbersome structure of the original form of the Bradford Hill [7] criteria in an epidemiological setting. These were developed for clinical studies in which experimental data give much more easily assessable conclusions in general. As more fully discussed in Tweedie and Mengersen (in preparation), Rothman [120] and Susser [160], there are a number of issues that do not fit easily into this framework:

1. The role of statistical significance of results is not easily incorporated, and we have had to consider this as part of the *strength of association* criterion; the above-mentioned authors advocate consideration of this as a separate issue.
2. The role of poor study design in epidemiology and consideration of other aspects of study and data quality are also not well catered for; we have considered these under the *strength of association*, *specificity* and *consistency* criteria, where they do play a part, but they should perhaps be considered as independent criteria.
3. Specificity, which is a criterion of considerable impact in the clinical literature on causality [161, 162], is not totally relevant, as this case study shows; it is implausible that most epidemiological relationships will be specific, and many of the issues we considered under this heading were really ones of study design and should perhaps be considered in that context.

The related issue of existence of confounding factors (or alternative explanations of observed results) is also not well covered by the Hill criteria and, again, might be treated separately.

4. The usual force of experimental evidence, which one might expect to encompass the use of intervention, is not valid in this context, and its role needs careful consideration; there can be a large gap between the model populations for which such experiments are available and the human populations to which they are extrapolated.

Nonetheless, the use of some systematic framework for evaluation of causality seems to be much more desirable than the ad hoc approach used widely in various reviews. To see the difference in approaches, one should contrast the Glantz and Parmley [10, 11] reviews or, more glaringly, the somewhat superficial OSHA report [5] with the recent report of the Australian NH&MRC [6], which evaluates the status of the various criteria on a basis similar to that described herein. The NH&MRC report [6] reaches conclusions different from those we give in this paper, but at least it is possible to consider the areas of difference and to obtain a clear picture of the scientific strengths of the agreement and disagreement within such a framework.

5.2. The causal argument: general population

Within this framework, forced though it may sometimes be, we have considered substantial sets of data related to the possible causal association of IHD and exposure to ETS. On the basis of the analyses in this paper we have drawn the following conclusions for the overall population exposed to ETS:

1. There is a reasonable case for biological plausibility of a causal association. This is, however, a weak test and one that is usually passed in any context where study has been seen as worthwhile.

2. The experimental data do not support the second of Hill's criteria. At best there is a possibility of aggravation of existing IHD as discussed below.

3. The overall strength of association, however one calculates it, is well under the level that supports causality [133], especially after allowance for bias has been made. We have demonstrated that the overall RR estimate of 1.24 for mortality may be reduced after accounting for publication bias alone, and both estimates for mortality and morbidity may be further reduced after accounting for other biases. All of these estimates are below the values of 1.5–2.0 and above, seen as close to "strong" by most authorities in the field, and after such adjustment for bias they may not be statistically significant at the 5% level.

4. The exposure-response argument is not established at all as indicated by our evaluation.

5. The consistency argument is not clear-cut.

6. There is clearly a lack of specificity in this area, and this seems to be universally acknowledged. Although (unlike many authors) we do not feel that a lack of specificity of itself means that a relationship is not causal, it does mean that a very serious attempt to consider possible confounding is needed.

7. The analogy criterion and the coherency criterion present substantial problems. It appears to us that the effects of active and passive smoke are well documented as being very different in this area, and this lack of analogy may explain the lack of coherence acknowledged by most authors.

The interpretation of fulfilment of Hill's criteria is somewhat subjective. Glantz and Parmley [11] review epidemiological studies concerned with the association between ETS and IHD and provide an overview of the various biological mechanisms that might cause this association, and they accept without further evaluation the assertion by Wells [15] and Kristensen [163] that the link is causal. The report of the Australian NH&MRC [6] (Table 6.6) evaluates the status of the various criteria and, despite acknowledging that the criteria are at best weakly met in some areas, nonetheless still concludes that an excess risk caused by exposure to ETS has been demonstrated.

Our contribution has been to provide a much more detailed critique of the available material, both biological and epidemiological, and, in our opinion, this leads to perhaps one of the nine tests being passed (biological plausibility), perhaps five about which there is insufficient or mixed evidence (biological gradient,experimental evidence, coherence, analogy, temporality) and three that we believe are actually failed (strength, consistency, specificity). Overall, this seems to us to indicate that one can at most say there is very weak support at the current time for this association across the general population.

5.3. Relation to other reviews

Other published reviews on the association between IHD and ETS exposure come to a variety of conclusions based on much of the material we have reviewed [1, 4, 5, 6, 9–13, 15, 110, 114, 120, 154, 164–166]. On the basis of comprehensive summaries of eight relevant studies available at the time, Lee [110] concludes that there is no causal relationship between ETS exposure and IHD. This is in contrast to Steenland [9] and Glantz and Parmley [10], who, on the basis of virtually the same set of studies, assert the existence of a causal relationship. In further reports, Glantz and Parmley [11] and Law et al. [13] reassert this causal relationship on the basis of both epidemiological and biological evidence. This is supported by the NH&MRC [6] review but is in direct contrast to that of Gori [12], who challenges the existence of a causal relationship and concludes that "the weight of evidence continues to falsify the hypothesis that ETS exposure might be a risk factor."

The OSHA report [5] also reviews these epidemiological studies. In an open review, Tweedie (unpublished manuscript, 1994) notes that the support claimed for a

positive association in the report is actually much more ambiguous. For example, the OSHA report asserts that 5 of the 11 studies of spousal smoking give statistically significant elevated relative risks, and all are increased, whereas, as Tweedie notes, only 2 are significant and 3 are actually less than unity. Apart from the study of He et al. [99], none of those that considered workplace smoking is unequivocal and one of them [95] is negative.

Why do these reviews come to conclusions different from those we have reached? This is one of the benefits of using the causal criteria described herein: they do provide a framework to consider such conflicts. First, we can look at the biological criteria. Glantz and Parmley [10, 11], Law et al. [13], the OSHA report [5] and the NHMRC report [6] find support for causality in these papers, although not independently; some reviews base conclusions on previous reviews. We differ herein in that, in our view, the animal evidence has been accepted almost uncritically. Apart from any serious evaluation of the weaknesses of the studies, there is an acceptance that many effects demonstrated in animals, such as (for example) the increase in fatty streaks in the papers by Zhu et al. [61], are indicative of increased risk of IHD in humans. In some cases these interpretations should be queried, given the published information. The assertion by Glantz and Parmley [10, 11] of no threshold in the increased infarct sizes observed in Zhu et al. [61] and the consequent assertion that these increases hold at levels of ETS exposure relevant to humans, is one such example. In other cases it is no doubt a matter of opinion as to how these studies should be interpreted, but it seems clear that one needs to consider them carefully rather than accepting them uncritically.

Second, we must consider the epidemiological criteria. Again, a number of reviews are not independent. Glantz and Parmley [10, 11] and the OSHA report [5], for example, essentially repeat the analysis of Wells [15]. In considering strength of association, Wells [15] supports a larger overall value than we do, primarily by using the EPA report [127] methodology, which provides a large adjustment for background exposure, an approach that has been reviewed critically (see Gross [149] above and Taylor and Tweedie [167]). However, regardless of the approach taken, the reviews do not find, as we do, that an overall RR that is nowhere near 2.0 is unconvincing (even though in other areas, such as the carcinogenicity of EMF, an RR of less than 3.0 has been rejected as too weak by, for example, the EPA). There is also a substantial difference between our assessment of exposure-response, which we find is not established overall. This is contrary to the analysis reported by Law et al. [13]. However, we feel that other reviews have not taken adequate notice of the variability in these sets of data and have accepted sometimes inaccurate statements by authors about the support for exposure-response in the individual papers.

Third, we need to examine the evidence from experimental and epidemiological sources combined. In particular, the sometimes facile analogy between mainstream and passive smoking is one that clearly presents some problems of coherence, and our discussion gives one way at least of coming to a resolution of this difficulty.

Finally, we note that one of the values of the causal criterion approach is that it does force attention on all of the criteria rather than allowing a reviewer to select the one or two aspects that might support a position in either direction. Thus, due weight must be given, e.g., to the lack of coherence (or analogy), the lack of specificity and the lack of real consistency that are ignored in some other reviews. Of course, even this framework can lead to differing outcomes. The recent NH&MRC report [6] does use much the same set of criteria we use herein. The authors note most of the same epidemiological outcomes that we do, such as the lack of coherence and the low strength of the association, although they consider only a small number of the sets of experimental data that we have evaluated, and they accept exposure-response with the unsupported statement that a dose-response effect is evident in several studies. Despite this same framework, they find that the data support a causal association, whereas we do not. Presumably at this point, one must agree that there is, as we well know, a subjective aspect to the overall evaluation of the criteria, even when the same material is considered.

5.4. The causal argument: pre-existing IHD

For the particular sub-population with pre-existing IHD, we find that stronger associations may apply. Indeed, one of the strengths of this review is in distinguishing between such a group and the general population. In this sense we find:

1. The biological plausibility seen in the general situation is of course maintained in this sub-population.
2. The experimental data are more supportive of an effect in this sub-population; although the acute effects that can be demonstrated, such as endothelial loss and platelet aggregation, have an impact on the disease process that can only be conjectured, they are consistent with a biological mechanism that would affect those with pre-existing disease.
3. There is virtually no existing epidemiological data of which we are aware that will give information on the strength of association in this sub-population. It is possible that the observed relative risks could be a mixture of an association sufficiently strong as to support causality in those with pre-existing conditions and the lack of any association in those without such conditions.
4. The exposure-response data are also consistent with a "threshold" effect such as that described in the experimental data above.

By considering the experimental data, we are led in this situation to a plausible but as yet untested situation. We believe that it is reasonable on the basis of the data seen

thus far to hypothesize that there may be real exacerbation of risk in those with pre-existing IHD.

To prove this, we clearly need epidemiology studies different from those we currently have available. The experimental data show that we need information on the real effect in populations who have pre-existing disease. For this, one needs to consider the relative risk, or perhaps the survival time to the next incident, of such populations with both exposure and non-exposure to ETS. Although this is clearly a somewhat sensitive population on which to collect data, our analysis lends clear support to such further research as being worthwhile.

5.5. Causality and public policy

On the application of his tests, Hill [7] stated "On scientific grounds the evidence is there to be judged on its merits and the judgement should be utterly independent of what hangs on it. It's another question entirely to ask what is involved in the decision."

It is important to realise that here we are only considering the scientific support for a causal association between IHD and exposure to ETS. It seems clear to us that the association, if present at all, is weak, and, in principle, satisfaction of Hill's criteria may be almost impossible with such small relative risks and such disparate data.

One may question the need for such rigour. For example, the overall association may not be statistically significant (due, say, to study size) but may be deemed to be clinically significant. Similarly, even if statistical significance is supported, the consequent inferences or actions must be contingent on the other tests of the observed result, which may, for example, be due to confounders that are not relevant to the statistical tests.

The actions taken on the basis of the assessment of any association will differ according to need, whether it be tort, public policy, support for further research or comparative assessment. In all cases, however, it is essential that proper attribution is made. Assertion that an action has been taken on the basis of scientific support for a causal relationship requires rigorous scientific justification of such support, whereas if an action is undertaken on the basis of other reasons, then a different level of rigour may be expected or required. One may well take action about exposure to ETS on the basis of quite different measures than a purported causal relationship with IHD, but it is important that one understand and detail the basis for such action. Conclusions and extrapolations made in the absence of such analyses [5] should be treated with considerable caution.

Quite substantial inferences are made and actions taken on the basis of these evaluations. Attributable risk computations [5, 10, 11], are cited as the foundation for tort and public policy. Such estimates are based on a number of assumptions, the most important of which is that there is indeed a causal relationship; without this basis, one may well have nothing but a statistical artefact. (Of course, other assumptions on which these computations are based may also be called into question [8, 167].)

Inferences made on the basis of epidemiological and biological studies are only as sound as the estimates and models on which they are based. It is important that the assumptions underlying them (such as causality) be justified and that they be accompanied by substantial sensitivity analyses, which indicate the range of estimates that could be generated under alternative and equally supported models.

The United States Surgeon General's review [1] (p.106) stated that "more detailed characterisation of exposure to ETS and specific types of IHD associated with this type of exposure are needed before an effect of involuntary smoking on the etiology of IHD can be established." In our opinion, this statement remains valid, and we see our identification of the sub-population with existing IHD as a group potentially at risk as being one step towards such detailed characterisation.

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